TEMPTIME

*The World Leader in Time-Temperature Indicators*

# Information Package for HEATmarker® VVMs


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## Foreward:

In December 2006, TEMPTIME Corporation submitted a 510(k) Pre-market notification to the U.S. FDA requesting permission to introduce the HEATmarker® Time Temperature Indicator into the U.S. market as a product that could be used with other approved medical devices. In so doing, TEMPTIME expanded the list of available products to include additional time and temperature limits. Since these new product codes utilize the same basic technology and follow the same design as the VVM, a single set of product specifications was developed to include both these new codes as well as the original four VVMs.

This Technical Information Package was intended to provide information specific to the VVM. The *General Specifications for HEATmarker® Time Temperature Indicators* is included to give a transparent view to the details of the TEMPTIME specifications for the VVM. All TEMPTIME VVMs conform to the WHO PQS Performance Specifications for Vaccine Vial Monitors (WHO/PQS/E06/IN05.1).

It is also important to note that while the specifications include a list of products that cover a range of time and temperature profiles, the inventory position and lead time for these newer offerings may not have been established as yet. Please contact your TEMPTIME Sales professional for additional information on these non-VVM products.

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**PQS performance specification**

WHO/PQS/E06/IN05.1
Original: English
Distribution: General

**TITLE: Vaccine Vial Monitor**

| | |
|---|---|
| *Specification reference:* | E06/IN05.1 |
| *Product verification protocol:* | E06/IN05.VP.1 |
| *Date of origin:* | 30 November 2006 |
| *Date of last revision:* | Replaces PIS specification E6/IN.5 rev. 25.03.2002 |

**Contents:**



## 1. Scope:

This specification describes the performance requirements for a *Vaccine Vial Monitor (VVM)* suitable for application to a vaccine vial by a vaccine

manufacturer. The product is used to indicate the cumulative heat exposure of a vial of vaccine so that health workers know whether the cumulative heat history of the product has exceeded a pre-set limit.

## 2. Normative references:

EMAS: *European Union Eco-Management and Audit Scheme.*
ISO 9001: 2000: *Quality Management Systems – Requirements.*
ISO 14001: 2004: *Environmental management systems - Requirements with guidance for use.*
ISO 2859-1: 1999: *Sampling procedures for inspection by attributes - Part 1: Sampling schemes indexed by acceptance quality limit (AQL) for lot-by-lot inspection.*

## 3. Terms and definitions:

AQL: Acceptance Quality Limit
Active surface: A time-temperature sensitive colour patch whose reaction rate closely matches the stability profile of the vaccine to which the VVM is attached[1].
End point: The point at which time-temperature exposure has altered the colour of the active surface so that it exactly matches the reference surface. At this point, and thereafter, the vaccine should no longer be used.
In writing: means communication by letter, fax or email.
Legal Manufacturer: The natural or legal person with responsibility for the design, manufacture, packaging and labeling of a product or device before it is placed on the market under his own name, regardless of whether these operations are carried out by that person himself or on his behalf by a third party.
Montreal Protocol: Montreal Protocol on Substances that Deplete the Ozone Layer.
OD: Optical Density.
Reference surface: A colour patch against which the colour of the active surface can be directly compared.
Reaction rate: The rate at which the active surface responds to time-temperature exposure.
Reseller: A commercial entity, licensed to act on behalf of a Legal Manufacturer, and which carries product liability and warranty responsibilities no less onerous than those carried by the Legal Manufacturer.
Start point: The colour of the active surface of the VVM at the time when the VVM is received by the vaccine manufacturer[2].
VVM: Vaccine Vial Monitor comprising, as a minimum, an active surface, a reference surface and the substrate to which these are applied by the VVM manufacturer.

[1] It is the vaccine manufacturer's responsibility to match the stability profile of their vaccine to the time-temperature profile of one of the four VVM types described in clause 4.2.6 of this specification.

[2] It is the vaccine manufacturer's responsibility to store the VVMs correctly to prevent any change in the start OD during the period elapsing between the time of receipt of the VVM to the time of its application to the filled vaccine vial.

## 4. Requirements:

4.1 *General:* Vaccine Vial Monitor suitable for application to a vaccine vial by a vaccine manufacturer.

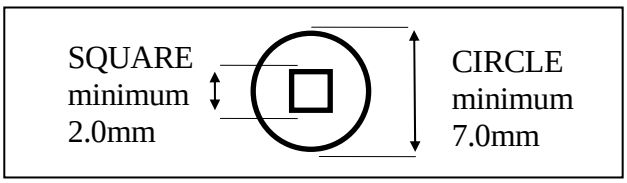
The principal purpose of this product is to warn health workers when the cumulative heat exposure of a vial of vaccine has exceeded a pre-set limit, beyond which the vaccine should not be used. This is defined as the end point.

Before the end point is reached, changes in the appearance of the VVM are used to alert health workers to the fact that heat exposure has occurred. Heat-exposed vials can then be used in preference to those that have not been exposed.

4.2 *Performance:*

*4.2.1* *Format and dimensions:* The VVM is a circle of colour, minimum diameter 7.0mm with a square of colour, minimum dimensions 2.0 x 2.0mm positioned in the centre of the circle (See Figure 1). Whatever dimensions are chosen, the ratio of the area of the square to the area of the circle (including the square) is to be at least 0.1:1. `

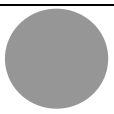
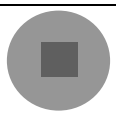
**Figure 1. Format and dimensions of VVM**




*4.2.2* *Design:* The circle of the VVM comprises a static, reference surface and the square comprises the active surface. The colour change of the active surface is limited to a change of shade, from light to dark. Any colour is permitted for the VVM design, but changes in hue are not permitted.

*4.2.3* *Colour density change:* The colour density change of the indicator is illustrated in the Figure 2 below. At the start point the colour of the square is lighter than the circle. The end point is indicated when the colour of the square matches the circle. The end point is exceeded when the colour of the square is darker than the circle. The following clauses describe the colour change in more detail.

**Figure 2. The colour density change of the indicator**

| | | |
|---|---|---|
| Start point |  | Square lighter than circle |
| End point |  | Square matches the circle |
| End point exceeded |  | Square darker than the circle |

Note: the central square is the active surface.

*4.2.4 Colour at start point and end point:*

- At the start point, the colour density of the square as measured by an Xrite Model 404 GS or GSX colour reflection densitometer, or later qualified model, must be lighter than the colour shade of the circle by a difference of at least 0.25 OD densitometer units[3].
- The end point is reached when the difference in the average colour density obtained from readings at least two different points on the circle and the colour density of the square is 0.00 OD, as measured by the densitometer. The end point is exceeded when the colour of the square is darker than the colour of the circle.
- The specifications for the Start R-I and the Indicator OD are shown in Table 1.

**Table 1: Start R-I and Indicator OD**

| VVM Category | Start R-I | Indicator OD |
|---|---|---|
| VVM30: White or Clear Liner | 0.54 ± 0.11 | 0.11 ± 0.04 |
| VVM30: Brown Liner | 0.51 ± 0.11 | 0.14 ± 0.04 |
| VVM14: White or Clear Liner | 0.44 ± 0.09 | 0.12 ± 0.04 |
| VVM14: Brown Liner | 0.41 ± 0.09 | 0.15 ± 0.04 |
| VVM7: White or Clear Liner | 0.44 ± 0.09 | 0.12 ± 0.04 |
| VVM7: Brown Liner | 0.41 ± 0.09 | 0.15 ± 0.04 |
| VVM2: White or Clear Liner | 0.34 ± 0.07 | 0.15 ± 0.05 |
| VVM2: Brown Liner | 0.31 ± 0.06 | 0.18 ± 0.05 |

*4.2.5 Homogeneity of the reference surface:* The colour density of one 2mm diameter portion of the circle must be within 0.03 OD of the colour density at any other two 2mm diameter portions of the circle, when measured with a colour densitometer.

*4.2.6 Variation of the reference surface within the lot:* The colour density of one 2mm diameter portion of the reference circle of one sample must be within

[3] Note: The specification for the Start R-I and the Indicator OD values, the Reference Ring Specification and OD limits found in this document are based on measurements with a X-rite Model 404 GS or GSX colour reflection densitometer calibrated to the standard TEMPTIME colour reflection reference card or to a secondary card calibrated to the TEMPTIME card. Measurements taken with other instrumentation or an X-Rite Model 404 GS or GSX colour reference densitometer calibrated to an X-Rite colour reflection reference card will require a conversion factor.

0.03 OD of the colour density of the reference circle of any other sample within the same lot.

*4.2.7* *Reference surface colours:* The colour of the reference area is specified in Table 2.

**Table 2: Reference surface colours**

| VVM Category | Reference Ring Specification |
|---|---|
| VVM30: White or Clear Liner | 0.65 ± 0.12 |
| VVM30: Brown Liner | |
| VVM14: White or Clear Liner | 0.56 ± 0.10 |
| VVM14: Brown Liner | |
| VVM7: White or Clear Liner | |
| VVM7: Brown Liner | |
| VVM2: White or Clear Liner | 0.49 ± 0.09 |
| VVM2: Brown Liner | |

*4.2.8* *VVM reaction rates:* Reaction rates are specific to four different models of VVM, relating to four groups of vaccines according to their heat stability at two specific temperature points (See Table 3).

**Table 3: VVM reaction rates by category of heat stability**

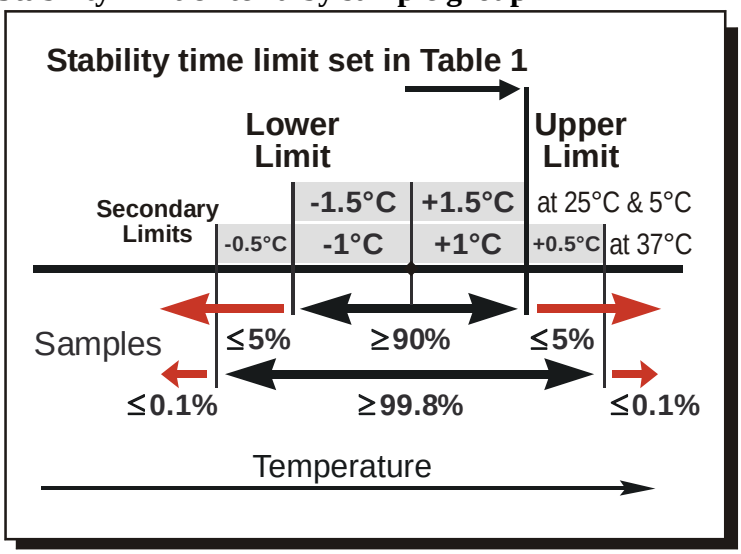
| Category (Vaccines) | No. of days to end point at +37°C | No. of days to end point at +25°C | Time to end point at +5°C |
|---|---|---|---|
| **VVM 30:** High Stability | 30 | 193 | > 4 years |
| **VVM 14:** Medium Stability | 14 | 90 | > 3 years |
| **VVM 7:** Moderate Stability | 7 | 45 | > 2 years |
| **VVM 2:** Least Stable | 2 | N/A* | 225 days |

**VVM (Arrhenius) reaction rates determined at two temperature points*

- **At the +37°C specifications, RH 33% +/-5% and RH 75% +/-5%:** At least 90% of VVMs tested should reach the end point at the maximum time in the range of 36 ±1°C. Further, secondary limits are applied to restrict how far beyond the primary specification the TTIs are allowed to be. At least 99.8% of VVMs tested should reach the end point at the maximum time in the range of 36 ±1.5°C.

- **At the 5°C and +25°C specifications (ambient humidity in submerged foil/polythene pouch**): At least 90% of VVMs tested should reach the end point at the maximum time in the range of the specified temperature ±1.5°C.
- **Tolerance:** A tolerance is allowed in the above tests for up to 5% of VVM samples tested to reach the end point at a temperature above the upper limit and 5% at a temperature below the lower limit (See Figure 3).

**Figure 3. Stability limit criteria by sample group**




- **Allowable range of end points:** Table 4 defines the allowable range of end points such that 90% of a production lot must reach the end point at the specified time within a range of ±1°C and that 99.8% of the lot must reach end point within a range of ±1.5°C.

**Table 4: Allowable range of end points**

| VVM Type | Primary Limits: ±1°C measured at upper limit (including OD tolerance) | | Secondary Limits: ±1.5°C measured at upper limit (including OD tolerance) | |
|---|---|---|---|---|
| | Lower Limit | Upper Limit | Lower Limit AQL=0.1% | Upper Limit AQL=0.1% |
| VVM30 | -0.19 | 0.03 | -0.24 | 0.06 |
| VVM14 | -0.15 | 0.03 | -0.18 | 0.06 |
| VVM7 | -0.11 | 0.03 | -0.13 | 0.05 |
| VVM2 | -0.09 | 0.03 | -0.10 | 0.04 |

*4.2.9* *Global Measurement Accuracy:* The allowable total error for measuring the difference between the colours of the circle and square is ± 0.03 OD when using an X-Rite 404 GS(X) colour reflectance densitometer, or later qualified model. The measurement error for a single measurement is ± 0.02 OD. Major sources of error are instrument error, both for the circle and the square, repeatability, and variation in end point caused by an allowed temperature variation of ± 0.2°C.

*4.2.10* *Water Bath Precision and Control:* The VVMs should be tested in water baths controlled to within ± 0.2°C. (Any additional 0.1°C variation in temperature control requires an allowance for additional measurement error.)

*4.2.11* *Reversion:* The indicator must not revert to a lighter colour at any point in its life when exposed to conditions likely to be found during normal use. After the endpoint is reached, the square must remain the same colour as the circle or become darker than the circle.

*4.2.12 Integrity of VVMs:*

The integrity of VVMs depends on the presentation of the vaccine:

- **For liquid vaccines:** The VVM will be permanently attached to the vaccine vial, even after the vial has been opened and must remain readily observable before, after and during use. Prior to opening, the VVM should not be removable: it should resist removal from the vaccine vial as much as a label meeting current requirements.
- **For freeze dried vaccines:** The VVM will be attached to the vaccine vial or ampoule and must remain readily observable until the vial or ampoule is opened but not observable after opening. Prior to opening, the VVM should not be removable: it should resist removal from the vaccine vial as much as a label meeting current requirements.

The performance of the VVM should not be changed by soaking in water for 8 hours. Water-exposed samples should conform to within +/-0.04 OD units.

4.3 *Traceability:* Each roll of VVMs must be labeled with its product identity (part number) together with its lot number[4].

4.4 *Physical characteristics:* Overall dimensions: As clause 4.2.1, Figure 1.

4.5 *Interface requirements:* None.

4.6 *Human factors:* The colour change must be monotonic in its response to cumulative heat exposure within the limits of the allowed variation. The observer must be able to distinguish between an unchanged indicator, a 50% colour change and the end point of the indicator.

4.7 *Materials:* The exposed surface of the VVM must not endanger human health. The materials of the VVM must be non-toxic and non-irritant. The VVM must meet any requirements in force concerning toxicity of labels or packaging in the country of manufacture.

4.8 *Reliability:* All batches of the product must be warranted to conform to the requirements of this specification.

4.9 *Servicing provision:* The product is to be maintenance-free.

4.10 *Disposal and recycling:* The product will be disposed of in conjunction with the vial to which it is attached.

4.11 *Instructions:* An instruction insert, providing vaccine manufacturers with all necessary storage, handling and application directions and traceability directions (with reference to clause 4.3) is to be supplied with every carton. The insert is to be printed in English. If any vaccine manufacturer requires an instruction insert in an additional language, this will be a matter for independent negotiation between the VVM manufacturer and the vaccine manufacturer.

[4] Vaccine manufacturers must keep records of the lot number of the VVMs affixed to each individual batch of vaccine.

4.12 *Training:* No requirement.

4.13 *Verification:* In accordance with PQS Verification Protocol **E06/IN05.VP.1.**

**5. Packaging:**
Materials used for packaging the finished product are to be free of CFC compounds as defined in the Montreal Protocol.

**6. On-site installation:**
VVMs will be applied to vaccine vials by vaccine manufacturers.

**7. Product dossier:**
The legal manufacturer or reseller is to provide WHO with a pre-qualification dossier containing the following:

- Dossier examination fee in US dollars.
- General information about the legal manufacturer, including name and address.
- Unique identification reference for the product type.
- Full specifications of the product being offered, covering all the requirements set out in this document, including details of product marking and traceability.
- Details of the legal manufacturer's internal AQL sampling procedures in respect of ISO 2859-1: 1999.
- Certified photocopies of the legal manufacturer's ISO 9001 2000 quality system certification.
- Where relevant, certified photocopies of the legal manufacturer's ISO 14001 certification, EMAS registration or registration with an equivalent environmental audit scheme. Conformity with an environmental audit scheme is not mandatory; however preference will be given to manufacturers who are able to demonstrate compliance with good environmental practice.
- Where available, laboratory test report(s) proving conformity with the product specifications.
- A minimum of five samples of each of the four types of VVM shipped with frozen icepacks, together with instruction insert in English language.
- Indicative cost of the product per 10,000, per 100,000 units and per 1,000,000 units EXW (Incoterms 2000).

**8. On-site maintenance:**
Not applicable.

**9. Change notification:**
The legal manufacturer or reseller is to advise WHO in writing of any changes which adversely affect the performance of the product, in relation to any of the requirements set out in this specification, after PQS pre-qualification has taken place.

**10. Defect reporting:**

The legal manufacturer or reseller is to advise WHO and the UN purchasing agencies in writing in the event of safety-related product recalls, component defects and other similar events.

| Revision history: | | | |
|---|---|---|---|
| Date | Change summary | Reason for change | Approved |
| 14 Mar 06 | Test procedure redrafted with general amendments to the form of wording but not to the content. Normative references, definitions and additional clauses added. | To achieve conformity with PQS documentation standards | UK |
| 29 Nov 06 | General revisions | Following consultation with industry | UK (30 November 2006 - PQS secretariat) |
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# General Specifications for HEATmarker® Time Temperature Indicators (TTIs)

## REVISION RECORD

**Original (Rev 1) Prepared By: S. Feldman**

| REVISION / APPROVAL HISTORY | | | | | |
|---|---|---|---|---|---|
| **Revision Number** | **Description** | **Document Revision Date** | **Revised by** | **Effective/ Issue Date** | **Distributed by / Date** |
| 1 | New | N/A | N/A | 23Feb07 | JCP 23Feb07 |
| 2 | Reference PQS product verification protocol WHO/PQS/ IN05.VP.1 30Nov06, PQS performance specification WHO/PQS/ IN05.1 30Nov06.Add definition for "Active Surface", use Reference Surface and Active Surface to replace reference ring and active area or indicator, max of 3 text colors,Ship by and Use by Dates. Made appropriate grammatical corrections | 6-Mar-07 | B.DePalma | 14Jun07 | CFC14Jun07 |
| 3 | Changed section 6.19.1.6 to "The use by date for the lot is applied to the corrugated backing inside the polyethylene packing pouch." | 13Aug07 | CFC | 27 Aug 07 | 27 Aug 07 AMK |
| **4** | **Changed section 6.19.1.6 removed"for the lot is applied to the corrugated backing inside the polyethylene packing pouch." When referring to "Use-by-Date"** | **08 Nov 07** | **HI** | | |
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# General Specifications for HEATmarker® Time Temperature Indicators (TTIs)

**1.** Purpose:

HEATmarker® TTIs are self-adhesive devices that can be applied to any temperature-sensitive products. The HEATmarker® TTI is a device that monitors the temperature exposure over time for individual containers of a medical product, whether a vial, pouch or unit carton. The HEATmarker® TTI provides a visual indication of when the heat exposure of the product has exceeded a pre-set limit, at which and after which the product should not be used.

**2.** Scope:

This specification applies to HEATmarker® TTIs that will be used by a health care provider to distinguish between medical products that have been or have not been exposed to a specific time and temperature profile of interest. TTIs are available in different categories based on their rate of change at specified time and temperature profiles.

**3.** References:

3.1. PQS Independent type-testing protocol WHO/PQS/IN05.VP.1 30Nov06
3.2. PSSD Spec Sheet db1
3.3. PQS performance specification WHO/PQS/IN05.1 30Nov06
3.4. QCLP P023c HEATmarker® Release Protocol for VVMs
3.5. QCLP P026 HEATmarker®Release Protocol for Non-VVMs
3.6. QCLM Recommended Testing Instructions
3.7. QCLI Calibration of a Densitometer
3.8. ARTI Artwork Instructions

**4.** Definitions:

4.1. Optical Density (OD) – a logarithmic measure of the intensity of a specific wavelength of light reflected from a target area. A “darker” area will reflect less light and therefore have a higher optical density.

4.2. Reference Surface – the static area of color on a TTI against which the color or OD of the Active Surface of the TTI is compared.

4.3. Active Surface - the color changing area in the shape of a square on a TTI whose color or OD is compared to the Reference Surface of the TTI,

**5.** Functional Requirements:

5.1. Intended use:

The HEATmarker® TTI is intended to be used by a health care provider to distinguish between medical products that have been or have not been exposed to or above a specific time and temperature profile of interest.

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# General Specifications for HEATmarker® Time Temperature Indicators (TTIs)

5.2. Indications for use:

When affixed to a medical product by a health care provider (user), the HEATmarker® TTI indicates, via a permanent color change, if a medical product has exceeded a selected time-temperature profile of interest to the user. HEATmarker® TTIs are available in different categories based on their rate of change at specified time and temperature profiles. The user selects the appropriate HEATmarker® TTI from among available models, following the instructions and referring to the tables in the accompanying labeling.

5.3. Design:

The visible surface of the indicator contains an area of color-changing material (Active Surface, see Figure 1) surrounded by an area of fixed color (Reference Surface, see Figure 1). The HEATmarker® TTI varies from start point (light) to end point (dark), when the inner Active Surface reaches the same color as the fixed Reference Surface. The color change is limited to a change of shade, from light to dark.

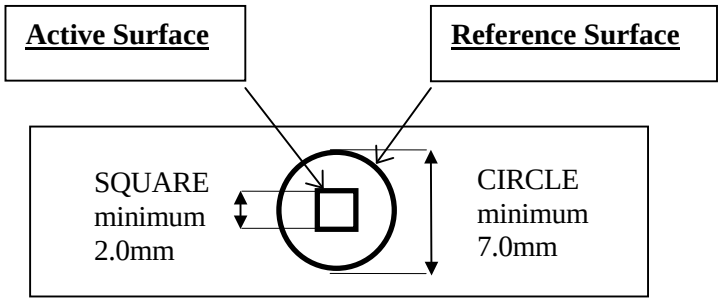


***Figure 1. Format and dimensions of TTI***

6. Performance Requirements:

6.1. Format and Dimensions:

6.1.1. As diagrammed in Figure 1, the dimensional requirements of the individual TTI are established as minimum specifications.

6.1.1.1. Minimum Diameter of Reference Surface circle = 7.0 mm.

6.1.1.2. Minimum width and length of Active Surface square= 2.0 mm.

6.1.1.3. Ratio of the area of the square to the area of the circle ≥ 0.1.

6.1.2. HEATmarker® TTIs are manufactured in two types:

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# General Specifications for HEATmarker® Time Temperature Indicators (TTIs)

6.1.2.1. The HEATmarker® TTI dot is manufactured on a polyolefin substrate with a clear over-laminate material. This over-laminate protects the underlying inks and adds stiffness to the indicator.

6.1.2.2. The HEATmarker® TTI can also be printed in combination with customized text and artwork (supplied by the customer). This type of product is manufactured on a paper substrate without an over-laminate.

6.1.2.2.1. The dimensional requirements of customized TTIs are specified by the client, subject to the following limitations:

6.1.2.2.1.1. Length and width are typically specified in millimetres with a tolerance of ± 0.5 mm.

6.1.2.2.1.2. The gap between the die cut TTIs is a minimum of 1.0 mm.

6.1.2.2.1.3. The dimensions of the Active Surface of the label remain as defined in 6.1.1.

6.1.2.2.1.4. Font size can be no less than 3 point.

6.1.2.2.1.5. There is a maximum of three text colors.

6.1.2.2.1.6. There is a difference of at least 0.5 mm between the text and the TTI.

6.1.2.2.1.7. Additional requirements are as specified in ARTI Artwork Instructions.

6.1.3. The “HEATmarker” trademark will be printed on each HEATmarker® TTI, along with the corresponding category designation.

6.2. Color:

The color of the HEATmarker® TTI is measured using an X-Rite 404 GS(X) color reflection densitometer calibrated according to TEMPTIME procedure *QCLI Calibration of a Densitometer*. This device measures reflected color density and is capable of giving readings for cyan, magenta and yellow colors. The OD of the HEATmarker® TTI is based on the cyan measurement and is reported in OD units.

**Note**: The specification for the Start R-I and the Active Surface OD values, the Reference Surface Specification and OD limits found in Tables 2 and 3 are based on measurements with a X-Rite Model 404 GS or GSX color reflection densitometer calibrated to the standard TEMPTIME color reflection reference card or to a

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# General Specifications for HEATmarker® Time Temperature Indicators (TTIs)

secondary card calibrated to the TEMPTIME card. Measurements taken with other instrumentation or a X-Rite Model 404 GS or GSX color reflection densitometer calibrated to an X-Rite color reflection reference card will require a conversion factor.

6.2.1. Start Point:

The start point is defined as the OD value of the Active Surface of the HEATmarker® TTI at the time of manufacturing by TEMPTIME. At the start point, the difference in OD between the Reference Surface and the Active Surface (R-I) is defined by a minimum specification.

6.2.1.1. Reference Surface OD – Active Surface OD ≥ 0.25 OD units.

6.2.1.2. The absolute OD of the Active Surface at the start point is defined in Table 3.

6.2.2. End point:

The end point is reached when the difference in the average OD obtained from reading at least two different points on the Reference Surface and the OD of the Active Surface is 0.00 OD. The end point represents the point at which and after which the product to which the HEATmarker® TTI is affixed has exceeded its pre-set time and temperature limits and should no longer be used. The end point is exceeded when the color of the Active Surface is darker than the color of the Reference Surface.

6.2.2.1. At end point, Reference Surface OD – Active Surface OD = 0.00 OD units.

6.3. Reaction rates:

HEATmarker® TTI categories vary based on the time – temperature profile they are designed to meet. The categories are listed along with their specified time and temperature parameters in Table 1.

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# General Specifications for HEATmarker® Time Temperature Indicators (TTIs)

***Table 1: TTI Lifetime by category***

| Category | Temperature | Time | |
|---|---|---|---|
| | | Days | Months |
| F3 | 5°C | 91 | 3 |
| F6 | 5°C | 182 | 6 |
| F9 | 5°C | 273 | 9 |
| F12 | 5°C | 365 | 12 |
| F24 | 5°C | 730 | 24 |
| F36 | 5°C | 1095 | 36 |
| CT2 | 22.5°C | 60 | 2 |
| CT3 | 22.5°C | 91 | 3 |
| CT4 | 22.5°C | 121 | 4 |
| CT6 | 22.5°C | 182 | 6 |
| CT9 | 22.5°C | 273 | 9 |
| CT12 | 22.5°C | 365 | 12 |
| CT24 | 22.5°C | 730 | 24 |
| CT36 | 22.5°C | 1095 | 36 |
| VVM2 | 37°C | 2 | N/A |
| VVM7 | 37°C | 7 | |
| VVM14 | 37°C | 14 | |
| VVM30 | 37°C | 30 | |

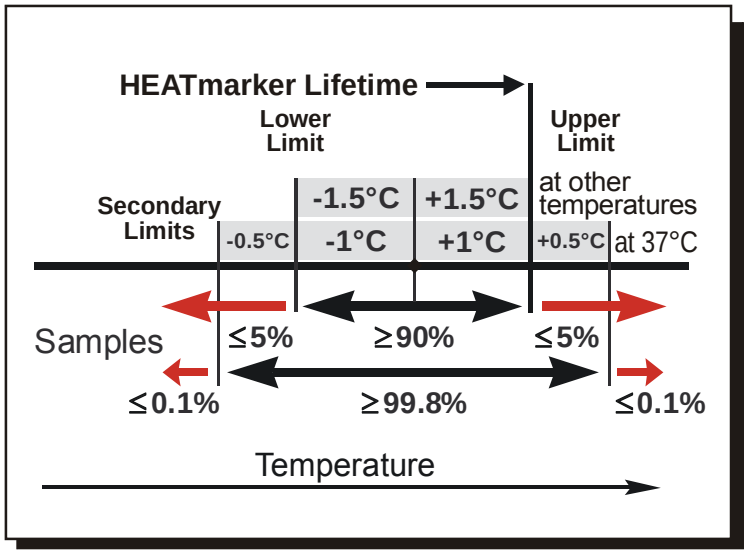


***Figure 2. HEATmarker® TTI Specifications***

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# General Specifications for HEATmarker® Time Temperature Indicators (TTIs)

6.3.1. Specification limits

Specifications for HEATmarker® TTIs are based on establishing a specified time and temperature as the upper limit of performance. The nominal or target for TTI performance is set at 1°C or 1.5°C less and the lower limit 2°C or 3°C less, depending on the specification temperature. For example, the F3 category would have a target specification of 91 days at 3.5°C ± 1.5°C.

At the limits of performance, the acceptable quality level (AQL) is defined as 5%. This means that no more than 5% of the HEATmarker® TTIs tested at the lower temperature can reach end point and no more than 5% of the HEATmarker® TTIs tested at the higher temperature can fail to reach end point. See figure 2 for a graphical representation of the specification limits.

It is known that the color change associated with HEATmarker® TTI performance is linked to the combined effects of time and temperature. At a higher temperature of storage for a given time, the rate of color development is higher. Similarly, at a given temperature for a longer storage time, more color is developed. The relationship between changes in time and temperature is defined by the activation energy.

The time for a HEATmarker® TTI to reach the end point at any temperature can be calculated from the activation energy, which is determined from the mid-points of the ranges at any two temperatures.

The equation that describes how a change in temperature changes the time to reach the end point is:

$$Time_2 = Time_1 \bullet e^{-\left(\frac{E_a}{\mathrm{R}}\right)\bullet\left(\frac{1}{T_1}-\frac{1}{T_2}\right)}$$

where $Time_n$ and $T_n$ are the corresponding time and Kelvin temperature pairs, $E_a$ is the activation energy, and R is the gas constant.

6.3.2. HEATmarker® TTI Testing

HEATmarker® TTIs are tested by measuring the OD range at the end point. In practice, manufactured lots of HEATmarker® TTIs are tested at a constant temperature. With the performance limits based on temperature, the measurable OD limits are calculated. The OD is measured directly at the important upper time limit of the specified temperature, and the OD calculation is used for the less important lower limit. At the upper time limit the OD values should always be

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# General Specifications for HEATmarker® Time Temperature Indicators (TTIs)

0.00 plus the allowable measurement tolerance of 0.03 OD. Additional test considerations are discussed in section 6.5.

6.3.3. Secondary limits

A secondary set of OD limits are also applied to reduce the possibility of HEATmarker® TTIs that are well beyond the specification limits being accepted. With the 5% AQL at either end of the specification, the secondary limits serve to limit just how far beyond specification the HEATmarker® TTIs are allowed to be. These limits are calculated similarly to the primary limits.

As some of the categories in the list have specified time limits extending several months, testing can be done at a higher temperature to reduce the time to end point. Once the activation energy is known, the temperature relationship defined above can be used to identify the test time at the higher temperature to decrease the time needed for testing.

***Table 2: OD limits by category***

| | | | Primary Limits | | Secondary Limits | |
|---|---|---|---|---|---|---|
| Category | Test Temperature (°C) | Test Time (days) | Lower limit | Upper limit | Lower limit | Upper limit |
| F3 | 12 | 32.8 | -0.11 | 0.03 | -0.12 | 0.05 |
| F6 | 20 | 19.7 | -0.09 | 0.03 | -0.11 | 0.05 |
| F9 | 20 | 27.0 | -0.11 | 0.03 | -0.13 | 0.05 |
| F12 | 20 | 32.8 | -0.10 | 0.03 | -0.12 | 0.05 |
| F24 | 25 | 31.0 | -0.11 | 0.03 | -0.12 | 0.05 |
| F36 | 30 | 19.1 | -0.10 | 0.03 | -0.11 | 0.05 |
| CT2 | 30 | 19.4 | -0.14 | 0.03 | -0.16 | 0.06 |
| CT3 | 30 | 29.1 | -0.19 | 0.03 | -0.23 | 0.06 |
| CT4 | 30 | 38.8 | -0.20 | 0.03 | -0.24 | 0.07 |
| CT6 | 37 | 21.1 | -0.17 | 0.03 | -0.21 | 0.06 |
| CT9 | 37 | 31.6 | -0.21 | 0.03 | -0.26 | 0.07 |
| CT12 | 37 | 40.8 | -0.21 | 0.03 | -0.26 | 0.07 |
| CT24 | 45 | 26.6 | -0.16 | 0.03 | -0.20 | 0.06 |
| CT36 | 45 | 35.3 | -0.10 | 0.03 | -0.12 | 0.05 |
| VVM2 | 37 | 2 | -0.09 | 0.03 | -0.10 | 0.04 |
| VVM7 | 37 | 7 | -0.11 | 0.03 | -0.13 | 0.05 |
| VVM14 | 37 | 14 | -0.15 | 0.03 | -0.18 | 0.06 |
| VVM30 | 37 | 30 | -0.19 | 0.03 | -0.24 | 0.06 |

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# General Specifications for HEATmarker® Time Temperature Indicators (TTIs)

6.3.4. HEATmarker® TTI Sampling

HEATmarker® TTIs are manufactured in rolls of up to 20,000 per roll. During manufacturing, 12 samples are taken from each roll, 6 at the beginning of the roll, and 6 at the end. Samples are tested at the appropriate time and temperature, and the OD difference between the Reference Surface and the Active Surface (R-I) areas is measured.

Due to roll-to-roll variability, individual rolls are dispositioned using a variables sampling method. Results are compiled and the standard deviation of results for each roll is computed. The average standard deviation ($s_{avg}$) of all rolls in the lot is then used in combination with a k-factor in the following equations to arrive at the roll acceptance limit:

$$\text{OD difference}_{avg} \text{ for the roll} < USL - k * s_{avg}$$
$$\text{OD difference}_{avg} \text{ for the roll} > LSL + k * s_{avg}$$

The k-factor is an acceptance constant used with variables sampling plans that takes into consideration the desired AQL and sample size. For an AQL of 5% and a sample size of 12, a k-factor of 1.17 is used. Any roll whose average OD difference does not meet the criteria above is culled from the lot.

6.4. Homogeneity of the static Reference Surface:

The color of the Reference Surface of the TTI is subject to variability due to variations in materials and manufacturing processes. This variability is broken down and quantified in two ways.

6.4.1. Variation within a single Reference Surface:

Within an individual Reference Surface, OD measurements taken at any three points around the circle must be within 0.03 OD units of each other.

6.4.1.1. Variation within a single Reference Surface ≤ 0.03 OD units

6.4.2. Variation of Reference Surface OD within a production lot:

The OD of one point on the Reference Surface of one TTI must be within 0.03 OD units of the OD of any other point on a Reference Surface within the same production lot.

6.4.2.1. Variation of Reference Surface OD within a production lot ≤ 0.03 OD units

6.4.3. Variation of average Reference Surface OD from lot to lot

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# General Specifications for HEATmarker® Time Temperature Indicators (TTIs)

6.4.3.1. The range of average OD values for the Reference Surface is defined in Table 3.

***Table 3: Limits for Active Surface Start OD and* Reference Surface *OD***

| Category | Active Surface Start OD (I) | Reference Surface OD (R) | Start R-I |
|---|---|---|---|
| F3 | 0.18 ± 0.05 | 0.49 ± 0.09 | 0.31 ± 0.06 |
| F6 | | | |
| F9 | | | |
| F12 | | | |
| F24 | 0.15 ± 0.04 | 0.56 ± 0.10 | 0.41 ± 0.09 |
| F36 | | | |
| CT2 | | | |
| CT3 | | | |
| CT4 | | | |
| CT6 | | | |
| CT9 | 0.14 ± 0.04 | 0.65 ± 0.12 | 0.51 ± 0.11 |
| CT12 | | | |
| CT24 | | | |
| CT36 | 0.14 ± 0.04 | 0.45 ± 0.08 | 0.31 ± 0.06 |
| VVM2, Brown Liner | 0.18 ± 0.05 | 0.49 ± 0.09 | 0.31 ± 0.06 |
| VVM2, White or Clear Liner | 0.15 ± 0.05 | | 0.34 ± 0.07 |
| VVM7, Brown Liner | 0.15 ± 0.04 | 0.56 ± 0.10 | 0.41 ± 0.09 |
| VVM7, White or Clear Liner | 0.12 ± 0.04 | | 0.44 ± 0.09 |
| VVM14, Brown Liner | 0.15 ± 0.04 | | 0.41 ± 0.09 |
| VVM14, White or Clear Liner | 0.12 ± 0.04 | | 0.44 ± 0.09 |
| VVM30, Brown Liner | 0.14 ± 0.04 | 0.65 ± 0.12 | 0.51 ± 0.11 |
| VVM30, White or Clear Liner | 0.11 ± 0.04 | | 0.54 ± 0.11 |

**Note**: The Active Surface Start OD and Start R-I values for the F and CT product categories are based on a brown liner; these values would be 0.03 OD units less on a clear or white liner.

6.5. Test considerations:

Analysis of the reactivity of the HEATmarker® TTIs is subject to the limitations of the tools and equipment used to carry out the testing. TEMPTIME has identified and quantified two potential sources of error.

6.5.1. Water bath precision:

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# General Specifications for HEATmarker® Time Temperature Indicators (TTIs)

HEATmarker® TTIs must be tested in sealed pouches submerged within thermostatically controlled isothermal water baths. The pouches shall be 5-mil heat-sealable foil-polyethylene pouches (MIL-B-131H, Type 1, Class1) or equivalent. The water bath must be capable of maintaining a set temperature to within ± 0.2°C.

**Note**: It is not recommended to use an incubator for testing the HEATmarker® TTIs since incubators typically lack the precise temperature uniformity required for testing.

6.5.2. Measurement accuracy:

The manufacturer of the X-Rite 404 GS(X) Color Reflection Densitometer specifies an accuracy of the instrument to within ± 0.02 OD units. Since multiple measurements are taken to determine the endpoint, these accuracy errors are accumulated. To accommodate the potential error associated with the water bath precision, a total error of ± 0.03 OD units is allowed.

6.6. Reversion:

A HEATmarker® TTI shall not revert to a lighter color at any point in its life when exposed to conditions likely to be found during normal use. After the endpoint is reached, the Active Surface shall remain the same color as the Reference Surface or become darker than the Reference Surface.

6.7. Legibility:

6.7.1. Any text printed on the TTI must be:

6.7.1.1. Free from missing characters.

6.7.1.2. Missing portions of a character must not interfere with the ability to identify the character.

6.7.1.3. Free from smudged print.

6.8. Integrity:

The HEATmarker® TTI shall be permanently attached to the product being monitored, even after the product has been opened, and remain readily observable before, after and during use. Prior to opening, the HEATmarker® TTI should not be removable: it should resist removal from the product as much as a label meeting current requirements.

6.9. Adhesion:

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# General Specifications for HEATmarker® Time Temperature Indicators (TTIs)

6.9.1. The HEATmarker® TTI is intended to be permanently adhered once it is applied to the product. Removal of the HEATmarker® TTI will cause damage such that it does not perform as specified or cannot be re-applied.

6.9.2. Adhesion can only be assured when the TTI is affixed to a clean and dry surface.

6.9.3. The Service Temperature range for the adhesive is limited to at least -30°C to 70°C.

6.9.4. Minimum application temperature is 10°C.

6.9.5. Peel adhesion as measured by removal from stainless steel should be at least 1.9 lbs/in.

6.10. Safety:

The exposed surface of the HEATmarker® TTI shall not be able to endanger human health. The materials of the VVM shall be non-toxic and non-irritating. The HEATmarker® TTI meets all requirements for toxicity of labels or packaging in the country of manufacture (USA).

6.11. Shelf Life and Storage:

6.11.1. HEATmarker® TTIs require storage at temperatures less than -24°C. When stored appropriately, the HEATmarker® TTI has a shelf life of 4 years. This will permit a “Ship-by-date” three years from the date of manufacture and a customer “Use-by-date” of one year from the date of packing.

6.11.2. HEATmarker® TTIs are very sensitive to light, including UV radiation and sunlight. HEATmarker® TTIs must be protected from light.

6.12. Splices

6.12.1. Number - Minimum of 95% of the rolls with 3 splices or less and not more than 5% of the rolls with up to 5 splices.

6.12.2. Location - located between 2 HEATmarker® TTIs and perpendicular to the release liner; located on the back of the release liner without exceeding its width. Visible on the edge of the rolls.

6.12.3. Type of splicing tape: Finite #570 or equivalent.

6.13. Production lots

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# General Specifications for HEATmarker® Time Temperature Indicators (TTIs)

6.13.1. The TTIs will be supplied in homogeneous lots, in compliance with these specifications.

6.13.2. Print must be uniform in color or intensity to within one Pantone shade.

6.13.3. Before implementation of any change of material, manufacturing process, product specification or delivery mode, TEMPTIME will inform the customer(s) of the proposed change at least 3 months before the implementation. This duration can be adjusted, shorter or longer, depending on the type of suggested modification, upon written request from the customer(s). Such changes will be subject to change control and qualified prior to implementation.

6.13.4. The materials used for production are qualified and accepted prior to use. They are stored in such a way as to ensure they will perform in accordance with applicable specifications.

6.13.5. Any important discontinuity in the manufacturing process must lead to changing the lot number. For example, lengthy downtime to make equipment repairs or a process adjustment beyond the limits established in the operating procedures.

6.13.6. TEMPTIME's internal traceability links manufactured batches/lots to the teams and equipment that made it, as well as to the raw material batches used for the manufacturing.

6.14. Documentation

6.14.1. All the data from the inspections will be recorded.

6.14.2. The results of final inspection will be reported on a certificate of analysis.

6.14.3. The documents corresponding to a specific production lot will be kept for 5 years.

6.15. Printing and Finishing

6.15.1. According to the good manufacturing practices, TEMPTIME does not perform any gang printing. Every time a new production lot is printed, a "line clearance" (line purge) is performed and recorded.

6.15.2. No HEATmarker® TTI that has come out from the production line will be reattached again on the release liner.

6.15.3. A maximum of 0.5% missing labels per roll will be accepted.

6.16. Common and Active inks

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# General Specifications for HEATmarker® Time Temperature Indicators (TTIs)

6.16.1. The Reference Surface ink and color-changing Active Surface ink is alcohol and water-insoluble.

6.16.2. Under proper storage and handling, the inks will remain adhered to the substrates upon which they are printed.

6.16.3. The Reference Surface ink and color-changing Active Surface ink will not stick the rolled labels to the silicon-coated release liner covering them.

6.16.4. A single batch of color-changing Active Surface ink is used to manufacture one production lot.

6.17. Shipping and delivery

6.17.1. Receipt constraints

6.17.1.1. TEMPTIME will choose the most convenient shipping configuration, depending on the size of the order and the destination.

6.17.1.2. Several different lots can be placed on the same pallet. Lots will be clearly identified.

6.17.1.3. Carbonic ice (dry ice) or frozen gel packs will be used in order to make sure the internal environment is suitable to avoid any measurable deterioration of the HEATmarker® TTIs for at least 72 hours.

6.17.1.4. The containers will be sealed at departure from TEMPTIME.

6.17.1.5. TEMPTIME will advise the customer of the container's anticipated date of arrival prior to shipment.

6.18. Labelling

6.18.1. Individual cartons will contain rolls of the same part number (product code) and lot number. The carton will be identified with a label stating:

6.18.1.1. TEMPTIME Corporation’s Name.

6.18.1.2. TEMPTIME’s part number (product code).

6.18.1.3. TEMPTIME’s lot number.

6.18.1.4. The use by date for the lot.

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# General Specifications for HEATmarker® Time Temperature Indicators (TTIs)

6.18.1.5. Customer's purchase order number and/or LC number.

6.18.1.6. Number of rolls per box.

6.19. Roll Identification

6.19.1. Each roll is identified with a label(s) placed on the first coil and inside the core. Each roll is then packed in a closed transparent polyethylene pouch with an internal cardboard base. The label(s) state(s):

6.19.1.1. TEMPTIME's part number (product code).

6.19.1.2. Manufacturing date (Julian date of manufacture is within the TEMPTIME lot number).

6.19.1.3. Number of labels per roll.

6.19.1.4. Sequential number of roll in the lot.

6.19.1.5. TEMPTIME's lot number.

6.19.1.6. **Use-by-Date**

6.20. Certificate of analysis

6.20.1. This document is specific to each lot and reports the results of the different inspections made by TEMPTIME to release the lot. It is included in the delivery. It states:

6.20.1.1. TEMPTIME's part number (product code).

6.20.1.2. Lot number of the delivery.

6.20.1.3. The average start R-I for the lot.

6.20.1.4. The percentage of results beyond the primary specification limits.

6.20.1.5. The distribution of the reactivity results from QC testing.

7. Interface Requirements:

7.1. Interfaces with different activities in application or use:

7.1.1. Hand Labeling - The HEATmarker® TTI is suitable for hand labeling applications.

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# General Specifications for HEATmarker® Time Temperature Indicators (TTIs)

7.1.2. Automatic Labeling - Customers with automatic labeling equipment should evaluate the HEATmarker® TTI for suitability with their labeling equipment. HEATmarker® TTI liner removal behavior will be affected by equipment variables such as line speed, and environmental conditions such as temperature and humidity.

7.2. Roll and packaging specifications

7.2.1. Release liner

7.2.1.1. The HEATmarker® TTIs are manufactured on a roll stock that includes either a white or brown silicon-coated, kraft paper or plastic liner material. The liner release forces are specified to be less than 25 grams per inch.

7.2.1.1.1. Liner release < 25 g/in.

7.2.1.2. The liner width is at least 1.0 mm beyond the HEATmarker® TTI on each side.

7.2.2. Roll features

7.2.2.1. The roll can be wound with either the labels facing outside or inside.

7.2.2.2. Quantity per roll: ± 0.5% of the roll count

7.2.2.3. Maximum roll external diameter: 45 cm or as specified by the client.

7.2.2.4. Core internal diameter may be specified by the client; standard core sizes are 76 mm ± 0.5 mm and 41 mm ± 0.5 mm.

7.2.2.5. Core material: cardboard.

7.2.2.6. Roll tension: sufficient to make sure the rolls perform correctly during handling operations, but not so high as to cause label deterioration (crease, wave, adhesive overflow).

7.2.2.7. In order to avoid any inopportune unrolling of the roll when handling it, the end of the roll will be held with a permanent adhesive label.

7.2.2.8. There must be no stress (e.g. wrinkles, deep die cuts) on the silicon-coated release liner and edges will be free of defects.

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# General Specifications for HEATmarker® Time Temperature Indicators (TTIs)

7.3. Application:

7.3.1. The HEATmarker® TTIs are intended to be applied to the following substrates:

7.3.1.1. Glass (e.g., glass vials).

7.3.1.2. Paperboard (e.g., primary or secondary packaging).

7.3.1.3. Plastic containers for which permeation of adhesive components is not a risk.

Note: Permanence of adhesion may be impacted by application to some plastic materials.

1

## Specifications for Vaccine Vial Monitors (VVM)

- PQS Performance Specification, Vaccine Vial Monitor (WHO/PQS/E06/IN05.1)
- General Specifications for HEATmarker® Time Temperature Indicators

2

## Testing Information

- Protocol for Testing and Releasing a Lot of HEATmarker® Vaccine Vial Monitors at 37°C
- Temperature Control Requirements for VVM End-point Determination

3

## Validation Information

- Practical Validation Procedures for Vaccine Vial Monitors
- PQS Independent Type-testing Protocol, Vaccine Vial Monitor (WHO/PQS/E06/IN05.VP.1)

4

## Practical Information

- Arrhenius graphs showing temperature-dependence for each category of VVM (-30 to +50°C and 0 to 40°C)
- Instructions for Use for Vaccine Vial Monitors
- Examples of full label and dot HEATmarker VVMs
- Effect of UV/Ambient Light Exposure on Color Development of HEATmarker® Vaccine Vial Monitors

5

## Commercial Information

- 2008 World-Wide Pricing Guide and General Conditions of Sale
- Special World-Wide Pricing Guide for UNICEF Tender Contracts (2007-2009) and General Conditions of Sale

2.1

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**DATE: 3-Apr-07**


# P023-C HEATmarker® Vaccine Vial Monitor (VVM) Release Protocol

## REVISION RECORD

**Original (Rev A) Prepared By: A.Klopper**

| REVISION / APPROVAL HISTORY | | | | | |
|---|---|---|---|---|---|
| **Revision Number** | **Description** | **Document Revision Date** | **Revised by** | **Effective /Issue Date** | **Distributed by / Date** |
| B | Updated protocol to include Type D VVMs and to include scanner testing | 10/20/00 | B DePalma | | |
| C | Updated release test method. | 1/23/02 | B DePalma | | |
| 4 | Changed document to be consistent with current formatting (Word.doc). Changed doc name to be consistent with FGDS General Specifications for HEATmarker Time Temperature Indicators, changed company name, added references & responsibilities | 3-Apr-07 | B DePalma | | |
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# P023-C HEATmarker® Vaccine Vial Monitor (VVM) Release Protocol

**1.** Purpose:

1.1. This procedure covers the methodology necessary to prepare and store samples at controlled temperatures and times, enter HEATmarker® Vaccine Vial Monitor (VVM) optical density or reflectance measurements into an IBM compatible computer, and process measurements into a spreadsheet format for analysis and release.

**2.** Scope:

2.1. Specifications for HEATmarker® VVMs are based on establishing a specified time and temperature as the upper limit of performance. The nominal or target for VVM performance is set at 1°C less and the lower limit 2°C less.

2.2. At the limits of performance, the acceptable quality level (AQL) is defined as 5%. This means that no more than 5% of the HEATmarker® VVMs tested at the lower temperature can reach end point and no more than 5% of the HEATmarker® VVMs tested at the higher temperature can fail to reach end point.

**3.** Reference:

3.1. PQS Independent type-testing protocol WHO/PQS/IN05.VP.1 30Nov06.
3.2. PQS performance specification WHO/PQS/IN05.1 30Nov06.
3.3. FGDS General Specifications for HEATmarker® Time Temperature Indicators (TTIs).
3.4. QCLI Calibration of a Densitometer.
3.5. QCLI Evaluation of QC Scanner Calibration and Verification.
3.6. QCLI Homogeneity Testing Instruction.
3.7. QCLI QC Scanner Instruction.
3.8. QCLM Recommended Testing Manual.
3.9. QCLI Densitometer Measurements using XRA Program.
3.10. QCLZ Scanner Access Import Template.
3.11. QCLI Final Release Test Evaluation
3.12. QCLI Calibration of thermometers and thermocouples.
3.13. SLTI Pharm Slitting and Numbering.

**4.** Responsibilities:

4.1. Operations personnel are responsible for the manufacture of the VVMs and submission of samples to Quality Control (QC).

4.2. QC personnel are responsible for the testing and release of the production lot.

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# P023-C HEATmarker® Vaccine Vial Monitor (VVM) Release Protocol

**5.** Safety:

5.1. Use caution around heating strip on heat sealer.

5.2. Use caution around the water baths which may be set to high temperatures (e.g. 70°C).

**6.** Definitions:

6.1. *Vaccine Vial Monitor* - A label containing a time and temperature sensitive color-changing material printed as a square surrounded by a non-variable circular reference color printed in the approved format and location on the label.

6.2. *Category* - A number used to designate the specification of the particular VVM.

6.3. *Lot* - A quantity of labels made from a specific quantity of active material with uniform composition, fabricated in a single production run, having a unique identification code. Special care must be given with respect to the definition of manufacturing “lot”. The terms *Batch* and *Lot* can be used interchangeably. A typical lot contains 500,000 to 3,000,000 VVMs.

6.4. *Shipment* - A quantity of VVM(s (not necessarily from one lot) that conforms to a set of specifications.

6.5. *Master Roll* - A large roll of labels produced on the printing press. This roll could contain from five to nineteen lanes.

6.6. *Finished Roll* - A roll of finished labels ready to be delivered to a customer. The typical roll contains from 5,000 to 20,000 labels.

6.7. *Densitometer* - an X-Rite 404 GS (or GSX) Color Reflection Densitometer used to measure the optical density of a color, using optical filters with wavelength bands corresponding to the printing process colors (CYAN, magenta, and yellow).

6.8. *Scanner* - A flatbed page scanner capable of scanning an area of at least 11x17" at a resolution of at least 100 dpi and connected to a PC for control and data storage. A scanner with these characteristics and verified accuracy and reproducibility is the Microtek 6400XL.

6.9. *Active Surface* - The square on the VVM which contains the temperature-sensitive color- changing (reactive) material.

6.10. *Reference Surface* - The static area of color on a VVM against which the active surface of the VVM is compared.

6.11. *Background* - The non-printed area of a full label VVM.

6.12. *Optical Density (OD)* - a logarithmic measure of the intensity of a specific wavelength of light reflected from a target area. A “darker” area will reflect less light and therefore have a higher optical density.

6.13. *Start Point OD* - The OD of the reference surface minus the OD of the active surface prior to any storage conditions that affect the color of the active surface portion of the label.

# P023-C HEATmarker® Vaccine Vial Monitor (VVM) Release Protocol

6.14. *End Point OD* - 0.00 for the OD of the reference surface minus the OD of the active surface.

**7.** Materials / Equipment:

7.1. *X-Rite Model 404 GS or GSX Color Reflectance Densitometer* - calibrated to the standard TEMPTIME color reflection reference card or to a secondary card calibrated to the TEMPTIME card. Measurements taken with other instrumentation or a X-Rite Model 404 GS or GSX color reflection densitometer calibrated to an X-Rite color reflection reference card will require a conversion factor.

7.2. *Microtek 6400XL Flatbed Scanner* - The scanner is used to measure the reflectance of several labels at the same time.

7.3. *110 lb. White Letter-size Index Card* - The VVMs will be set on a white index card when measuring.

7.4. *Personal Computer* - The computer is connected directly to the densitometer or scanner in order to store and analyze the indicator optical density data.

7.5. *Programs XRA.EXE and QC.EXE with spreadsheets XRA Kinetics Import and QCLZ Scanner Access Import Template* - XRA.EXE transfers measurement data from the densitometer to a database on a personal computer, and XRA Kinetics Import is an Excel spreadsheet that imports and analyzes the data. QC.EXE is used to scan the samples, and store the scanned values into a database, and QCLZ Scanner Access Import Template is a QuattroPro spreadsheet that imports and analyzes the data.

7.6. *Isothermal temperature-controlled chambers* - Fluid-filled chambers utilizing temperature controllers that maintain temperature to within ± 0.2 □C of nominal set point, e.g., Huber series of isothermal baths.

7.7. *Pouches* –5 mil heat sealable foil-polyethylene pouches (MIL-B-131H, Type 1, Class 1)[1]

7.8. *Heat sealer* - An impact sealer capable of heat sealing the indicators in the pouches so that VVMs do not get wet in the isothermal baths.

7.9. *Freezer* - A standard freezer capable of maintaining -18□C.

**8.** Procedure:

*8.1. Performance Check of Instrumentation*

8.1.1. The densitometer must be calibrated to the standard TEMPTIME color reflection reference card, or to a secondary card calibrated to the TEMPTIME card. Calibration is required every day that the densitometer is used, and the card should be recalibrated or replaced every 18 months. Refer to work instructions QCLI Calibration of a Densitometer.

[1]U.S. military specification

8.1.2. The scanner is calibrated for the type of label being measured by calculating the necessary parameters for converting the red, green, and blue measured reflectance values to the equivalent cyan OD measured by the densitometer for that label type. Refer to work instructions QCLI Evaluation of QC Scanner Calibration and Verification.

8.1.3. The temperature of the isothermal chambers should be monitored with a calibrated thermocouple or thermometer using a data logging system. Refer to work instructions QCLI Calibration of thermometers and thermocouples.

*8.2. Sample Preparation*

8.2.1. A full web width sample of the master roll at least seventy labels long in the web direction are removed from both the beginning and from the end of each finished roll during the slitting process, or from individual master rolls during the printing process. Refer to work instructions SLTI Pharm Slitting and Numbering.

8.2.2. A full web width consisting of six labels in length in the web direction from the beginning and a full web width consisting of six labels in length from the end of each finished roll are barcoded with B for beginning and C for core of the finished roll, sealed in pouches and submerged in the appropriate isothermal chambers (maximum of 25 samples sheets inside each pouch). The remaining sample sheets from each finished roll are stored in a freezer and are held as retains for a minimum of 6 years from date of manufacture. Refer to work instructions QCLM Recommended Testing Manual and SLTI Pharm Slitting and Numbering.

8.2.3. Due to UV light sensitivity of the indicator, tests are conducted with only brief exposure to ambient room lighting during the measurement process.

8.3. *Determination of the Start Point*

8.3.1. The samples, still attached to the release liner, are placed on a white index card.

8.3.2. The optical density (OD) of the active surface, reference surface, and background (if a full label) of one row of VVMs per every two master rolls are measured with a calibrated X-Rite 404 densitometer using the program XRA. The OD of the reference surface is an average of one measurement from the top or bottom of the ring, and one measurement from a side of the ring. The data is read and stored directly into a computer using the program XRA. Using macro library XRA Kinetics Import in Excel, the data is transferred into a spreadsheet file where analysis can occur.

8.4. *Measurement of the Samples*

8.4.1. When the Test Times are reached according to QCLM Recommended Testing Manual the samples are removed from the isothermal chamber and placed in a freezer until they are ready to be measured.

8.4.2. The samples are placed on a white index card.

8.4.3. The reference surface and the active surface for six labels from the beginning sample and six labels from the core sample of each roll are measured with a

densitometer using program XRA or a scanner. Refer to work instructions QCLI Densitometer Measurements using XRA Program, QCLI Calibration of a Densitometer, QCLI Evaluation of QC Scanner Calibration and Verification, QCLI Homogeneity Testing Instruction, QCLI QC Scanner Instruction, QCLZ Scanner Access Import Template and QCLI Final Release Test Evaluation.

8.4.3.1. The samples are stored in a freezer while outside the isothermal chamber, except when the measurement is being made. The measurement period for a group of labels takes no more than thirty minutes when using a scanner. This brief exposure to room temperature has no affect on the measured density. When using a densitometer, the person measuring the labels takes a sheet of samples representing approximately ten rolls out of the freezer. When the measurements are complete for that group, they are replaced in the freezer and another sample sheet is taken out and measured.

*8.4.4.* The data is transferred into a spreadsheet file using XRA Kinetics Import (for *densitometer data) or QCLZ Scanner Access Import Template (for scanner data).*

8.5. *Lot Release Acceptance Criteria*

8.5.1. The average start-point value must be 0.25 OD, with a tolerance of ±0.02.

8.5.2. The differences between the reference surfaces and active surfaces at the test time at the specified temperature are statistically analyzed to select rolls of labels that conform to the following specifications:

8.5.3. Specifications for HEATmarker® VVMs are based on establishing a specified time and temperature as the upper limit of performance. The nominal or target for VVM performance is set at 1°C less and the lower limit 2°C less.

8.5.4. At the limits of performance, the acceptable quality level (AQL) is defined as 5%. This means that no more than 5% of the HEATmarker® VVMs tested at the lower temperature can reach end point and no more than 5% of the HEATmarker® VVMs tested at the higher temperature can fail to reach end point. See figure 1 for a graphical representation of the specification limits.

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# P023-C HEATmarker® Vaccine Vial Monitor (VVM) Release Protocol

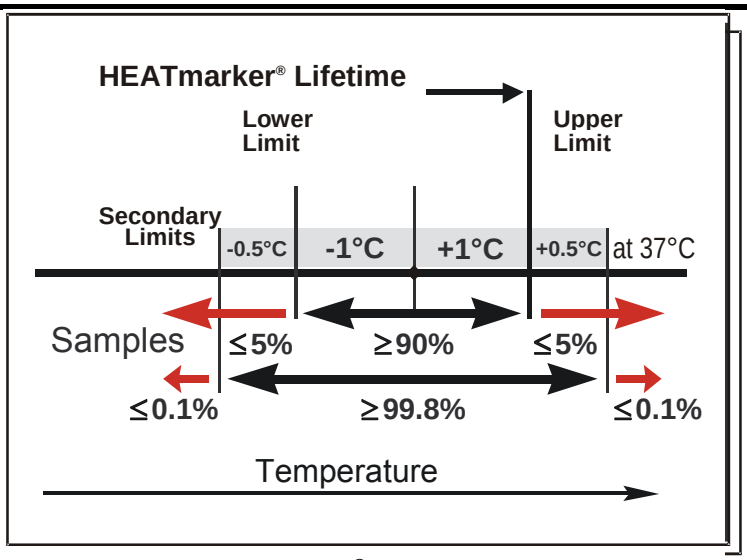



*Figure 1. HEATmarker® VVM Specifications*

8.5.4.1. A secondary set of OD limits are also applied to reduce the possibility of HEATmarker® VVMs that are well beyond the specification limits being accepted. With the 5% AQL at either end of the specification, the secondary limits serve to limit just how far beyond specification the HEATmarker® VVMs are allowed to be. These limits are calculated similarly to the primary limits. See table 1 for OD limits.

| | | | Practical Criteria for TEMPTIME Release | | | |
|---|---|---|---|---|---|---|
| | | | Primary Spec | | Secondary Limits | |
| Category | Test Temperature (°C) | Test Time (days) | Lower spec | Upper spec | Lower limit | Upper limit |
| VVM2 | 37 | 2 | -0.09 | 0.03 | -0.10 | 0.04 |
| VVM7 | 37 | 7 | -0.11 | 0.03 | -0.13 | 0.05 |
| VVM14 | 37 | 14 | -0.15 | 0.03 | -0.18 | 0.06 |
| VVM30 | 37 | 30 | -0.19 | 0.03 | -0.24 | 0.06 |

*Table 1. HEATmarker® VVM Test Temperature – Test Time- OD Limits*

8.6. *Data Presentation*

8.6.1. A Certificate of Analysis outlining the results of the release testing is supplied for each lot.

# TEMPTIME Corporation

## Temperature Control Requirements for VVM End-point Determination

TABLE OF CONTENTS



Original 07-Mar-2002

Revised 16-Oct-2007

Dr. Fred Grabiner and Dr. Thaddeus Prusik

# Temperature Control Requirements in VVM End-point Determination

## 1 Objectives

The objective of this study is to determine the effects of temperature control errors in measuring the optical density of VVMs at or near the end-point. VVM30 is used as the reference VVM for this discussion.

## 2 Introduction

VVMs are time-temperature indicators that darken as a function of cumulative temperature exposure. They are printed as a square of color-changing Indicator material (I) surrounded by a circle of a Reference color (R). The indicator gradually darkens with time, and the rate of darkening increases with the temperature. The VVM is considered to have reached its end point when the indicator is as dark as the reference. This can be quantitatively determined by measuring the difference between the optical densities (OD) of the reference and indicator with a color reflectance densitometer. Specifically, a VVM has reached or exceeded the end point when the OD of (R-I) $\geq$ 0.00 . For maximum uniformity the densitometer used is always an X-Rite model 404GS which has been calibrated either to a specific calibration card at TEMPTIME or to a secondary card which has been calibrated to the primary card. Measurements are generally in the cyan spectral range.

VVMs are measured after storage in constant-temperature water baths for specified times. The OD of a sample of a production lot is measured. The lot is acceptable if 90% of VVMs reach the end point in a time range specified by the WHO PQS Performance Specification, Vaccine Vial Monitor (WHO/PQS/EN06/IN05.1) of 30 November 2006 at a specific temperature.

Due to the variation of end point time with temperature, which is the basic function of a VVM, it is important to maintain the test temperature as close as possible to the specified temperature. The following analysis discusses the errors caused by improper temperature control, such as would occur by using an incubator instead of a water bath.

## 3 Error Analysis

### 3.1. Average Temperature of Water Bath

VVMs are tested by storing in constant-temperature baths for a specific time and then measuring their optical density. The time to reach the end-point is very sensitive to the temperature, and the ability of the bath to hold a constant temperature and the accuracy of measuring that temperature are extremely important to correctly determining the time when the VVM should reach its end-point.

The rate of color change of a VVM as a function of temperature is determined by the Arrhenius relationship:

$$k = A_0 e^{-\left(\frac{E_a}{RT}\right)} \quad \textbf{(1)}$$

where $A_0$ is a constant with the same time units as the rate constant k. T is expressed in degrees Kelvin (°C + 273). When R is set equal to 0.001987 kcal/(mole ● deg), then the activation energy, $E_a$, is given in units of kcal/mole.

This relationship can be used to calculate the change in the end-point time with temperature. A typical VVM30 has an activation energy of about 27.1 kcal/mole. For a test at 37° C, the average end-point should be at 26.25 days. If the OD changes linearly from 0.50 to 0.00 with these time-temperature conditions, equation (1) can be used to determine the days to end-point or the OD measured at 26.25 days as a function of temperature. The results are shown in Table 1 and in Figures 1 and 2 for the assumption that the temperatures have the average value shown with a cyclical variation of ±0.2°. A change of just 0.1°C changes the end point by 0.38 days (9.1 hours) or changes the OD measurement at the end point by 0.007 OD.

| TEMPERATURE | DAYS | OD AT 26.25 DAYS |
|---|---|---|
| 36.00 | 30.26 | 0.066 |
| 36.10 | 29.83 | 0.060 |
| 36.20 | 29.41 | 0.054 |
| 36.30 | 28.99 | 0.047 |
| 36.40 | 28.58 | 0.041 |
| 36.50 | 28.18 | 0.034 |
| 36.60 | 27.78 | 0.028 |
| 36.70 | 27.39 | 0.021 |
| 36.80 | 27.00 | 0.014 |
| 36.90 | 26.62 | 0.007 |
| 37.00 | 26.24 | -0.000 |
| 37.10 | 25.88 | -0.007 |
| 37.20 | 25.51 | -0.014 |
| 37.30 | 25.15 | -0.022 |
| 37.40 | 24.80 | -0.029 |
| 37.50 | 24.45 | -0.037 |
| 37.60 | 24.11 | -0.044 |
| 37.70 | 23.77 | -0.052 |
| 37.80 | 23.43 | -0.060 |
| 37.90 | 23.11 | -0.068 |
| 38.00 | 22.78 | -0.076 |

Table 1
Days to End-Point and OD at 26.25 Days

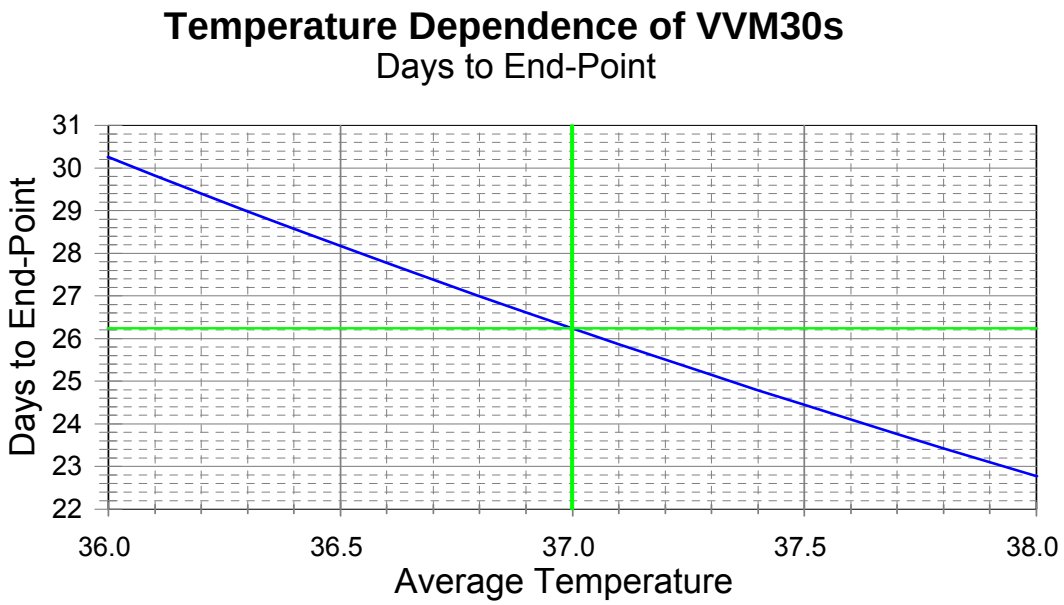



Figure 1.

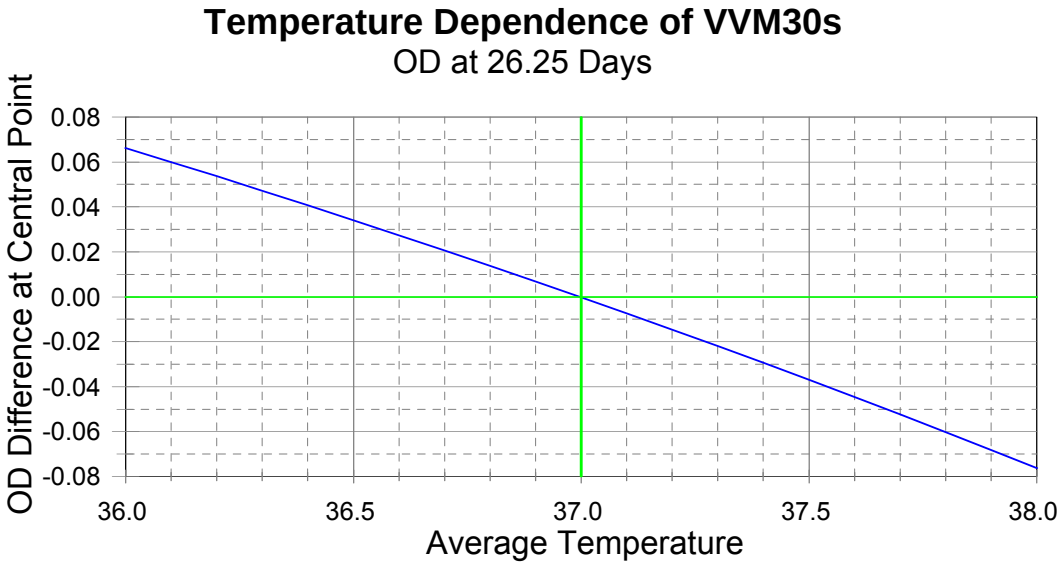



Figure 2.

### 3.2 Cyclical Temperature Changes

Even if the average temperature is correct, cyclical temperature changes around the average can increase the average reaction rate. As seen in equation 1, the reaction rate is not related linearly to temperature. Since increasing temperatures have greater effect on the reaction rate than decreasing temperatures, a cyclical temperature variation has a reaction rate slightly higher than the average temperature. The single equivalent temperature that would cause this reaction rate is called the mean kinetic temperature. If the temperature history is known, the mean kinetic temperature can be calculated from the individual temperatures by the following formula:

$$T_k = \frac{E_a / R}{-\ln\left(\frac{\sum_i [t_i \bullet \exp(-E_a / RT_i)]}{\sum_i t_i}\right)} \qquad (2)$$

where $T_i$ is the average temperature for time period $t_i$. This definition is equivalent to that for the mean kinetic temperature given in the U.S.P. [U.S.P. 23 (1995), p. 1941], modified to allow for unequal time intervals.

For a constant temperature bath, this effect should not be significant, though it would cause a measurable error in an incubator. For a sinusoidal temperature variation centered at 37°C for temperature control in some applications, they generally do not have sufficient temperature control for reliably testing VVMs.

## 4. COMPARISON OF WATER BATHS AND INCUBATORS

### 4.1 Temperature Control Capabilities

4.1.1. Although incubators are adequate for temperature control in some applications, they generally do not have sufficient temperature control for reliably testing VVMs.

4.1.2. The following table compares the temperature control capabilities of typical water baths and incubators:

| Control Capabilities | Water Bath | Incubator |
|---|---|---|
| Examples: | Huber CC1 K25 | Binder KB720 |
| Claimed Mean Temperature | ±0.01ºC | ±0.6ºC at 10°C |
| Claimed Cyclical Temperature Variations | ±0.01ºC | ±0.3°C |
| Claimed Temperature Uniformity | ±0.02ºC at 70ºC | ±0.4ºC at 37ºC |
| Internal Temperature Variations measured in baths and incubators from these companies at TEMPTIME Corporation | Temperature control of about ±0.1ºC maintained. Constant throughout the bath. | Temperature control of about ±1ºC. Generally varies throughout the incubator. Typically more than ±2ºC |

4.1.3 Although incubator manufacturers claim temperature variations close to that for water baths, this temperature control is difficult to obtain in practice. For example, in a Binder incubator at TEMPTIME, similar to the one listed above, the actual measured temperatures for a 39°C set point were 38.4°, 39.2°, and 38.5°, measured from near top to near bottom of the incubator.

## 4.2 Mean Temperature

4.2.1 A water bath with a stated accuracy of ±0.01°C can maintain in practice a mean temperature within ±0.2°C. This causes an uncertainty of ±0.014 in the final OD of a VVM30.

4.2.2 An incubator can maintain in practice a mean temperature within ±1°C. This causes an uncertainty of +0.066 to -0.076 OD, which is equivalent to an error of 3.5 to 4 days in the time to reach the end point for a VVM30.

## 4.3 Cyclical Temperature Variations

4.3.1 In a water bath, because the range in the temperature variation is small, the cyclical temperature variations are equivalent to the mean temperature variations, and do not cause a measurable OD change at the end point.

4.3.2 In an incubator the cyclical temperature variations are also equivalent to the mean temperature variations. In this case they can cause an additional error of 0.01 OD, due to the fact that the mean kinetic temperature is higher than the average temperature.

### 4.4 Internal Temperature Variations

4.4.1 In a water bath with proper flow characteristics there is no significant temperature variation in different locations of the bath. This can easily be tested, and any flow problems can be corrected.

4.4.2 In an incubator, there can be variations of several degrees in different locations inside the incubator. The control point temperature only applies exactly to the vicinity of the monitoring thermocouple. Different loading conditions, such as the presence of boxes, sample holders, etc., also change the airflow and can affect the temperature uniformity. It would be common for the location where the VVMs are tested to be 2° different from the set point, accounting for another variation of about ±0.07 OD for a VVM30.

## 5 Conclusions

VVM end-points are extremely sensitive to the storage temperature, which is a requirement of their function. It is vital to maintain proper temperatures in all measurement tests. The necessary temperature control is difficult, if not impossible, to maintain in an incubator, but is easily achieved in a laboratory constant-temperature water bath. According to the values in Table 1, testing in an incubator with an error of just ±1°C would introduce an error of the order of ±14% in end-point determination. At TEMPTIME Corporation, only temperature-controlled water baths are used for release tests.

1

## Specifications for Vaccine Vial Monitors (VVM)

- PQS Performance Specification, Vaccine Vial Monitor (WHO/PQS/E06/IN05.1)
- General Specifications for HEATmarker® Time Temperature Indicators

2

## Testing Information

- Protocol for Testing and Releasing a Lot of HEATmarker® Vaccine Vial Monitors at 37°C
- Temperature Control Requirements for VVM End-point Determination

3

## Validation Information

- Practical Validation Procedures for Vaccine Vial Monitors
- PQS Independent Type-testing Protocol, Vaccine Vial Monitor (WHO/PQS/E06/IN05.VP.1)

4

## Practical Information

- Arrhenius graphs showing temperature-dependence for each category of VVM (-30 to +50°C and 0 to 40°C)
- Instructions for Use for Vaccine Vial Monitors
- Examples of full label and dot HEATmarker VVMs
- Effect of UV/Ambient Light Exposure on Color Development of HEATmarker® Vaccine Vial Monitors

5

## Commercial Information

- 2008 World-Wide Pricing Guide and General Conditions of Sale
- Special World-Wide Pricing Guide for UNICEF Tender Contracts (2007-2009) and General Conditions of Sale

TEMPTIME

# PRACTICAL VALIDATION PROCEDURES FOR VACCINE VIAL MONITORS

***30 Mar 07***

## 1. Scope:

This document is intended to provide a guideline for VVM validation procedures to be performed by any vaccine manufacturer who introduces a new VVM or who uses VVMs for the first time. These guidelines comply with the practical application of sections of the specification for VVMs defined by WHO in *PQS Performance Specification, Vaccine Vial Monitor* WHO/PQS/E06/IN05.1, 30 November 2006, utilizing appropriate test equipment, procedures and acceptance criteria defined by WHO *PQS Independent Type-testing Protocol, Vaccine Vial Monitor* WHO/PQS/E06/IN05.VP.1, 30 November 2006.

The WHO Procedure WHO/PQS/E06/IN05.VP.1 is for independent laboratory validation studies.

## 2. Test conditions:

- The temperature of the water bath should be monitored throughout the test and a summary of the data included in the final report. The temperature stability and uniformity should be controlled within a tolerance of ±0.2°C. During tests in the water bath, VVMs should be heat-sealed in the pouches supplied by the VVM manufacturer. Three lots of 600 VVMs for each VVM reaction rate category to be tested should be delivered to the vaccine manufacturer. They should be packed in an insulated container with dry ice, and there should be residual dry ice on arrival at the vaccine manufacturer. The VVMs should be labelled with individual lot identification numbers and reaction rate category (2, 7, 14 or 30).
- The VVMs should be stored below -24°C in a freezer whose temperature is recorded continuously.
- When the samples are handled in preparation for the tests they should be removed from the freezer for the briefest period possible and immediately returned to storage below -24°C.
- VVM measurements should be made on a flat surface with the VVMs attached to the release liner (as supplied) and placed on the white card supplied by the VVM manufacturer.
- Due to UV light sensitivity of the indicator, tests should be conducted with only brief exposure to ambient room lighting during the measurement process, and these samples should be stored in the dark.
- Colour Measurements should be made with a colour reflection densitometer, X-Rite Model 404 GS or GSX calibrated to LifeLines standard, using the cyan color filter.

Reaction rates are specific to the four categories of VVM defined by the WHO *PQS Performance Specification, Vaccine Vial Monitor* WHO/PQS/E06/IN05.1, 30 November 2006, relating to different groups of vaccines according to their heat stability time limit (See Table 1 of the Specification).

*Table 1: VVM reaction rates by category of heat stability and temperature and time periods for testing (from PQS Performance Specification, Vaccine Vial Monitor* WHO/PQS/E06/IN05.1, 30 November 2006)

| **Category: (Vaccines)** | **No. days to end point at +37°C** | **No. days to end point at +25°C** | **Time to end point at +5°C** |
|---|---|---|---|
| **VVM30** HIGH STABILITY | 30 | 193 | > 4 years |
| **VVM14** MEDIUM STABILITY | 14 | 90 | > 3 years |
| **VVM7** MODERATE STABILITY | 7 | 45 | > 2 years |
| **VVM2** LEAST STABLE | 2 | NA* | 225 days |

**VVM (Arrhenius) reaction rates determined at 5 and 37 degrees C*

Unless otherwise specified, the two temperatures and time periods highlighted in Table 1 will be the agreed test period for testing each VVM category. VVMs will be tested at 75, 100, and 125% of the agreed test period at 37.0°C and at 60, 100 and 140% of the agreed test period at the second temperature (25.0°C for VVM30, VVM14, and VVM7; 5.0°C for VVM2).

## 3. Number of lots and number of samples

This Practical Validation Procedure recommends that three different lots of the same type of VVM should be used. In order to meet the requirements of this procedure, it is recommended that 600 VVMs of each lot be requested from TEMPTIME. Additional samples may be requested for other studies as required by the vaccine manufacturer.

*Table 2: Summary of tests and samples recommended*

| ***Test*** | ***Number of Samples*** | ***Notes*** |
|---|---|---|
| 4.1 Format and Dimensions | 20 | |
| 4.2 Starting Point | 50 | |
| 4.3 Homogeneity of the Start Point | -- | Data from 4.2 used for this test |
| 4.4.1 VVM Reaction Rate at 37°C 75% of time | 60 | VVM30 = 22.50 days<br>VVM14 = 10.50 days<br>VVM7 = 5.25 days<br>VVM2 = 1.50 days (36.0 hours) |
| 4.4.2 VVM reaction rate at 37°C – 100% of time | 60 | VVM30 = 30.00 days<br>VVM14 = 14.00 days<br>VVM7 = 7.00 days<br>VVM2 = 2.00 days (48.0 hours) |
| 4.4.3 VVM reaction rate at 37°C – 125% of time | 60 | VVM30 = 37.50 days<br>VVM14 = 17.50 days<br>VVM7 =8.75 days<br>VVM2 = 2.50 days |
| 4.5.1 VVM reaction rate at 2nd temperature (25°C for VVM7, 14, 30 or 5°C for VVM2) – 60% of time | 60 | VVM30 = 115.8 days<br>VVM14 = 54.00 days<br>VVM7 = 27.00 days<br>VVM2 = 135.0 days |
| 4.5.2 VVM reaction rate at 2nd temperature (25°C for VVM7, 14, 30 or 5°C for VVM2) – 100% of time | 60 | VVM30 = 193.0 days<br>VVM14 = 90.0 days<br>VVM7 = 45.0 days<br>VVM2 = 225.0 |
| 4.5.3 VVM reaction rate at 2nd temperature (25°C for VVM7, 14, 30 or 5°C for VVM2) – 140% of time | 60 | VVM30 = 270.2 days<br>VVM14 =126.0 days<br>VVM7 =63.0 days<br>VVM2 =315.0 days |

## 4. Tests to verify conformance of VVMs

### 4.1 Format and Dimensions (Active square and reference circle)

This Practical Validation Procedure recommends selecting a random sample of 20 VVMs (for each VVM category to be tested).

4.1.1 Measure the diameter (d) of the reference ring for each sample and record the result.

4.1.2 Measure the length of the indicator square (*l*) for each VVM and record the result.

4.1.3 Calculate the area of the reference ring ($A_{ref\ ring} = 3.14 * (d/2)^2$).

4.1.4 Calculate the area of the square ($A_{square} = l^2$)

NOTE: Annex 4.1 contains a sheet as an example for recording data of § 4.1.

***Acceptance criteria***

**"Reference ring of minimum diameter 7.0 mm. Active indicator square of minimum dimensions 2.0 x 2.0 mm positioned in the centre of the circle. The ratio of the area of the square to the area of the circle (including the square) is at least 0.1, whatever dimensions are chosen."[1]**

### 4.2 Starting point

This Practical Validation Procedure recommends that 50 samples be measured for the test. Each manufacturer should decide on the number of samples required to meet their sampling standard.

4.2.1 Place white card stock supplied with VVMs on a flat surface.

4.2.2 Select 50 samples of one lot of VVMs.

4.2.3 Place VVMs (while still attached to release liner) on the white card stock. This assures a good homogeneous background basis.

4.2.4 Read the active surface on each VVM sample using a calibrated colour densitometer (cyan mode) and record the result.

4.2.5 Repeat the measurement of the indicator two additional times and record the results.

4.2.6 Measure and record the OD of three different portions of the reference surface for each VVM. (NOTE: Care must be taken to assure that the reference ring measurements are made on the fully printed section of the ring, not the section that has the VVM type printed, as this will give a false reading).

NOTE: Annex 4.2 contains a sheet as an example for recording data of §4.2. This same sheet is also useful for §4.3.

[1] *PQS Performance Specification, Vaccine Vial Monitor* WHO/PQS/E06/IN05.1, 30 November 2006

***Acceptance criteria***

**"At the start point, the colour density of the square as measured by a colour densitometer, must be lighter than the colour shade of the circle by a difference of at least 0.25 OD densitometer units."[1]**

## 4.3 Homogeneity of the Indicator Start OD

The homogeneity of the indicator start point should be checked against requirement of *PQS Independent Type-testing Protocol, Vaccine Vial Monitor* WHO/PQS/E06/IN05.VP.1, 30 November 2006.

***Acceptance criteria***

**"The active surface readings for all samples should be within ±0.03 OD of the mean of the whole group."[2]**

4.3.1 Measurements recorded for §4.2 can be used for verification of conformance to this test procedure (see Annex 4.2)

If the requirements of § 4.1 through 4.3 are not met, the test should be halted and the VVM manufacturer contacted for a new batch of sample VVMs.

If the requirements of § 4.1 through 4.3 are met, the samples should be divided into six sets of 60 samples each for reaction rate tests described in § 4.4 and § 4.5.

The pouches[3] used for the study should be properly identified with the VVM lot and can be numbered 4.4.1, 4.4.2, 4.4.3, 4.5.1, 4.5.2, 4.5.3 corresponding to the reaction rate test conditions.

After the samples are placed in the pouch, the pouch should be sealed with the appropriate heat sealer to assure a watertight closure is made.

## 4.4 VVM reaction rate at +37°C at three time points - 75%, 100% and 125% of the stability limit.

Test times at 37°C corresponding to WHO *PQS Independent Type-testing Protocol, Vaccine Vial Monitor* WHO/PQS/E06/IN05.VP.1, 30 November 2006 are at 75%, 100% and 125% of the "stability limit" (WHO *PQS Performance Specification, Vaccine Vial Monitor* WHO/PQS/E06/IN05.1, 30 November 2006).

Three pouches should be prepared with 60 VVMs in each, one for each time point.

### 4.4.1 Test time = 75% of stability limit.

4.4.1.1 60 samples for the lot should be kept on the release liner, sealed in a pouch, and placed in a 37.0°C ±0.2°C water bath.

4.4.1.2 After storage in a controlled water bath at 37.0°C +/- 0.2°C for 75% of the stability limit for the type of VVM being tested (e.g. 22.50 days

[1] *PQS Performance Specification, Vaccine Vial Monitor* WHO/PQS/E06/IN05.1, 30 November 2006
[2] *PQS Independent Type-testing Protocol, Vaccine Vial Monitor* WHO/PQS/E06/IN05.VP.1, 30 November 2006
[3] 5 mil heat sealable foil-polyethylene pouches (MIL-B-131H, Type 1 Class 1 – supplied with the VVM samples

for VVM30), remove the VVMs from the pouch, place the VVMs on the white card supplied, and place them on a flat surface.

4.4.1.3 Three measurements of the OD at different sections of the reference ring are made on the first VVM and the average calculated.

4.4.1.4 Three measurements of the OD of the indicator of the first VVM are made and the average calculated.

4.4.1.5 The difference in the average indicator OD is subtracted from the difference in the average reference OD for each VVM (average OD reference – average OD indicator).

4.4.1.6 Steps 4.4.1.3 through 4.4.1.5 are repeated for each VVM.

***Acceptance criteria***

**"…at least 90% of VVMs tested should reach the end point within a range of time whose upper limit is shown in Table 1 or a period set by the vaccine manufacturer, based on published vaccine stability data, and whose lower limit is 25% below the upper limit."[1]**

**"A tolerance is allowed in the above tests for up to 5% of VVM samples tested to reach the end point after the upper limit and 5% before the lower limit ."[1]**

**At 75% of the time to the upper limit, at least 95% of the measurements (average OD reference – average OD indicator) for all VVMs must be greater than 0.00 when the allowed tolerance of +/- 0.04 OD is considered (see § Global Measurement Accuracy in** *PQS Performance Specification, Vaccine Vial Monitor* WHO/PQS/E06/IN05.1, 30 November 2006**).**

Note: Annex 4.4.1 contains a sheet as an example for recording data of §4.4.1

### 4.4.2 Test time = 100% of the stability limit.

4.4.2.1 60 samples for the lot should be kept on the release liner, sealed in a pouch, and placed in a 37.0°C ±0.2°C water bath.

4.4.2.2 After storage in a controlled water bath at 37.0°C +/- 0.2°C for 100% of the stability limit for the type of VVM being tested (e.g. 30 days for VVM30), remove the VVMs from the pouch, place the VVMs on the white card supplied, and place them on a flat surface.

4.4.2.3 Three measurements of the OD at different sections of the reference ring are made on the first VVM and the average calculated.

4.4.2.4 Three measurements of the OD of the indicator of the first VVM are made and the average calculated.

4.4.2.5 The difference in the average indicator OD is subtracted from the difference in the average reference OD for each VVM (average OD reference – average OD indicator).

4.4.2.6 Steps 4.4.2.3 through 4.4.2.5 are repeated for each VVM.

[1] *Specification for Vaccine Vial Monitors (VVM)* E6/IN5, 25 March 2002

***Acceptance criteria***

**"…at least 90% of VVMs tested should reach the end point within a range of time whose upper limit is shown in Table 1 or a period set by the vaccine manufacturer, based on published vaccine stability data, and whose lower limit is 25% below the upper limit."[1]**

**"A tolerance is allowed in the above tests for up to 5% of VVM samples tested to reach the end point after the upper limit and 5% before the lower limit ."[1]**

**At the upper time limit, at least 95% of the measurements (average OD reference – average OD indicator) for all VVMs must be less than or equal to 0.00 when the allowed tolerance of +/- 0.04 OD is considered (see § Global Measurement Accuracy in** *PQS Performance Specification, Vaccine Vial Monitor* WHO/PQS/E06/IN05.1, 30 November 2006)**.**

Annex 4.4.2 contains a sheet as an example for recording data of §4.4.2

### 4.4.3 Test time = 125% of stability limit.

4.4.3.1 60 samples for the lot should be kept on the release liner, sealed in a pouch, and placed in a 37.0°C ±0.2°C water bath.

4.4.3.2 After storage in a controlled water bath at 37.0°C +/- 0.2°C for 125% of the stability limit for the type of VVM being tested (e.g. 37.5 days for VVM30), remove the VVMs from the pouch, place the VVMs on the white card supplied, and place them on a flat surface.

4.4.3.3 Three measurements of the OD at different sections of the reference ring are made on the first VVM and the average calculated.

4.4.3.4 Three measurements of the OD of the indicator of the first VVM are made and the average calculated.

4.4.3.5 The difference in the average indicator OD is subtracted from the difference in the average reference OD for each VVM (average OD reference – average OD indicator).

4.4.3.6 Steps 4.4.3.3 through 4.4.3.5 are repeated for each VVM.

***Acceptance criteria***

**All of the measurements (average OD reference – average OD indicator) for each VVM should be less than or equal to 0.00 when the allowed tolerance of +/- 0.04 OD is considered (see § Global Measurement Accuracy in** *PQS Performance Specification, Vaccine Vial Monitor* WHO/PQS/E06/IN05.1, 30 November 2006).

Annex 4.4.3 contains example sheets for recording data.

## 4.5 VVM reaction rate at 2nd temperature (+25.0°C for VVM30, VVM14, and VVM7 or +5.0°C for VVM2) at three time points - 60%, 100% and 140% of the stability limit.

Test times at the second temperature (+25.0°C for VVM30, VVM14, and VVM7 and 5.0°C for VVM2) corresponding to WHO *PQS Independent Type-testing Protocol, Vaccine Vial Monitor* WHO/PQS/E06/IN05.VP.1, 30 November 2006 are at 60%, 100% and 140% of the "stability limit" (WHO *PQS Performance Specification, Vaccine Vial Monitor* WHO/PQS/E06/IN05.1, 30 November 2006).

Three pouches should be prepared with 60 VVMs in each, one for each time point.

### 4.5.1 Test time = 60% of stability limit

4.5.1.1 60 samples for the lot should be kept on the release liner, sealed in a pouch, and placed in a 25.0°C ±0.2 water bath for VVM30, VVM14, and VVM7 or in a 5.0°C ±0.2 water bath for VVM2.

4.5.1.2 After storage in a controlled water bath for 60% of the stability limit for the type of VVM being tested (e.g. 115.8 days for VVM30), remove the VVMs from the pouch, place the VVMs on the white card supplied, and place them on a flat surface.

4.5.1.3 Three measurements of the OD at different sections of the reference ring are made on the first VVM and the average calculated.

4.5.1.4 Three measurements of the OD of the indicator of the first VVM are made and the average calculated.

4.5.1.5 The difference in the average indicator OD is subtracted from the difference in the average reference OD for each VVM (average OD reference – average OD indicator).

4.5.1.6 Steps 4.5.1.3 through 4.5.1.5 are repeated for each VVM.

***Acceptance criteria***

**"At +25°C (ambient humidity in submerged plastic/foil pouch) at least 90% of VVMs tested should reach the end point within a range of time whose upper limit is shown in Table 1 for VVM30, VVM14 and VVM7 categories, or a period set by the vaccine manufacturer, based on published vaccine stability data, and whose lower limit is 40% below the upper limit."[1]**

**"At 5°C (ambient humidity in submerged plastic/foil pouch), at least 90% of VVM2 samples tested should reach the end point within a range of time whose upper limit is 225 days and whose lower limit is 40% below the upper limit."[1]**

[1] *Specification for Vaccine Vial Monitors (VVM)* E6/IN5, 25 March 2002

**"A tolerance is allowed in the above tests for up to 5% of VVM samples tested to reach the end point after the upper limit and 5% before the lower limit ."**[1]

**At 60% of the upper limit, at least 95% of the measurements (average OD reference – average OD indicator) for all VVMs must be greater than 0.00 when the allowed tolerance of +/- 0.04 OD is considered (see § Global Measurement Accuracy in** *PQS Performance Specification, Vaccine Vial Monitor* WHO/PQS/E06/IN05.1, 30 November 2006**).**

Annex 4.5.1 contains a sheet as an example for recording data of §4.5.1

### 4.5.2 Test time = 100% of stability limit

4.5.2.1 60 samples for the lot should be kept on the release liner, sealed in a pouch, and placed in a 25.0°C ±0.2 water bath for VVM30, VVM14, and VVM7 or in a 5.0°C ±0.2 water bath for VVM2.

4.5.2.2 After storage in a controlled water bath for 100% of the stability limit for the type of VVM being tested (e.g. 193.0 days for VVM30), remove the VVMs from the pouch, place the VVMs on the white card supplied, and place them on a flat surface.

4.5.2.3 Three measurements of the OD at different sections of the reference ring are made on the first VVM and the average calculated.

4.5.2.4 Three measurements of the OD of the indicator of the first VVM are made and the average calculated.

4.5.2.5 The difference in the average indicator OD is subtracted from the difference in the average reference OD for each VVM (average OD reference – average OD indicator).

4.5.2.6 Steps 4.5.2.3 through 4.5.2.5 are repeated for each VVM.

***Acceptance criteria***

**"At +25°C (ambient humidity in submerged plastic/foil pouch) at least 90% of VVMs tested should reach the end point within a range of time whose upper limit is shown in Table 1 for VVM30, VVM14 and VVM7 categories, or a period set by the vaccine manufacturer, based on published vaccine stability data, and whose lower limit is 40% below the upper limit."**[1]

**"At 5°C (ambient humidity in submerged plastic/foil pouch), at least 90% of VVM2 samples tested should reach the end point within a range of time whose upper limit is 225 days and whose lower limit is 40% below the upper limit."** [1]

**"A tolerance is allowed in the above tests for up to 5% of VVM samples tested to reach the end point after the upper limit and 5% before the lower limit ."** [1]

[1] *Specification for Vaccine Vial Monitors (VVM)* E6/IN5, 25 March 2002

**At the upper time limit, at least 95% of the measurements (average OD reference – average OD indicator) for all VVMs must be less than or equal to 0.00 when the allowed tolerance of +/- 0.04 OD is considered (see § Global Measurement Accuracy in** *PQS Performance Specification, Vaccine Vial Monitor* WHO/PQS/E06/IN05.1, 30 November 2006**).**

Annex 4.5.2 contains a sheet as an example for recording data of §4.5.2

### 4.5.3 Test time = 140% of stability limit

4.5.3.1 60 samples for the lot should be kept on the release liner, sealed in a pouch, and placed in a 25.0°C ±0.2 water bath for VVM30, VVM14, and VVM7 or in a 5.0°C ±0.2 water bath for VVM2.

4.5.3.2 After storage in a controlled water bath for 100% of the stability limit for the type of VVM being tested (e.g. 193.0 days for VVM30), remove the VVMs from the pouch, place the VVMs on the white card supplied, and place them on a flat surface.

4.5.3.3 Three measurements of the OD at different sections of the reference ring are made on the first VVM and the average calculated.

4.5.3.4 Three measurements of the OD of the indicator of the first VVM are made and the average calculated.

4.5.3.5 The difference in the average indicator OD is subtracted from the difference in the average reference OD for each VVM (average OD reference – average OD indicator).

4.5.3.6 Steps 4.5.3.3 through 4.5.3.5 are repeated for each VVM.

***Acceptance criteria***

**All of the difference measurements (average OD reference – average OD indicator) for each VVM should be less than or equal to 0.00 when the allowed tolerance of +/- 0.04 OD is considered (see § Global Measurement Accuracy in** *PQS Performance Specification, Vaccine Vial Monitor* WHO/PQS/E06/IN05.1, 30 November 2006**).**

Annex 4.5.3 contains a sheet as an example for recording data of §4.5.3

## 5. Reporting

This Practical Validation Procedure recommends issuing a final report after all testing is completed on three lots of each VVM.

The report of the tests should contain the following data and analyses:

- dimensional tolerances of the VVM (see Annex 4.1as an example);
- distribution of active surface (indicator) starting point readings (see Annex 4.2 as an example);
- distribution of the difference between the active surface and the reference ring color starting point readings (see Annex 4.2 as an example);
- distribution of reaction test readings (reference – indicator) at 37.0ºC and times (see Annexes 4.4.1, 4.4.2, and 4.4.3 as examples).
- distribution of reaction test readings (reference – indicator) at 25.0°C (VVM30, VVM14, and VVM7) or 5.0ºC (VVM2) and times (see Annexes 4.5.1, 4.5.2, 4.5.3 as examples).

As the VVMs are very sensitive to the temperature of the water bath, the report should contain the water bath temperature record showing conformance with the requirement of 37.0, 25.0 and/or 5.0 +/- 0.2ºC.

All average VVM measurements should be rounded to the nearest hundreth (0.01) of OD.

WHO/PQS/E06/IN05.VP.1
Original: English
Distribution: General

**PQS Independent type-testing protocol**

**TITLE: Vaccine Vial Monitor**

| | |
|---|---|
| *Product verification protocol:* | E06/IN05.VP.1 |
| *Applies to specification ref(s):* | E06/IN05.1 |
| *Date of origin:* | 30 November 2006 |
| *Date of last revision:* | Replaces PIS test procedure E6/PROC/5 dated 25.03.2003 |

**Contents:**



## 1. Scope:

This document describes the procedure for verifying the performance of vaccine vial monitors.

**2. Normative references:**

ISO/IEC 17025:1999 2005 *General requirements for the competence of testing and calibration laboratories.*
WHO/PQS /E06/IN05.1: *WHO Performance Specification for Vaccine Vial Monitors.*

**3. Terms and definitions:**

Active surface: A time-temperature sensitive colour patch whose reaction rate closely matches the stability profile of the vaccine to which the VVM is attached[1].
End point: The point at which time-temperature exposure has altered the colour of the active surface so that it exactly matches the reference surface. At this point, and thereafter, the vaccine is no longer suitable for useshould no longer be used.
In writing: means communication by letter, fax or email.
Legal Manufacturer: The natural or legal person with responsibility for the design, manufacture, packaging and labelling of a product or device before it is placed on the market under his own name, regardless of whether these operations are carried out by that person himself or on his behalf by a third party.
OD: Optical Density.
Reference surface: A colour patch against which the colour of the active surface can be directly compared.
Reaction rate: The rate at which the active surface responds to time-temperature exposure.
Reseller: A commercial entity, licensed to act on behalf of a Legal Manufacturer, and which carries product liability and warranty responsibilities no less onerous than those carried by the Legal Manufacturer.
Start point: The colour of the active surface of the VVM at the time when the VVM is applied to the vaccine vial received by the vaccine manufacturer[2].
VVM: Vaccine Vial Monitor comprising, as a minimum, an active surface, a reference surface and the substrate to which these are applied by the VVM manufacturer.

**4. Applicability:**

Type testing must be carried out by an independent ISO/IEC 17025 accredited testing laboratory, pre-qualified by WHO. On-site inspection of the legal manufacturer's production facilities will be carried out by WHO or by a consultant appointed by WHO for this purpose.

**5. Type-testing procedure:**

5.1 *Number of samples:* The Legal Manufacturer or Reseller must supply the testing laboratory with a full duplicate set of the Product Dossier already

[1] It is the vaccine manufacturer's responsibility to match the stability profile of their vaccine to the time-temperature profile of one of the four VVM types described in clause 4.2.6 of this specification.

[2] It is the vaccine manufacturer's responsibility to store the VVMs correctly to prevent any change in the start OD during the period elapsing between the time of receipt of the VVM to the time of application to the filled vaccine vial.

supplied to WHO in accordance with the requirements of specification clause 7. The following test samples are required for each VVM reaction rate category to be tested:

- 500 VVMs.
- Six test patches of the active surface. The 'test patches' of active surface must be at least 7 mm diameter, printed on the same backing paper as the VVM, but without the printed reference surface.

All samples must be in an active state. They must be packed in an insulated container with dry ice or frozen gel packs and there must be residual dry ice or partially frozen gel packs in the container when it arrives at the laboratory. The VVMs and test patches must be clearly labelled with individual identification numbers and the relevant reaction rate category (2, 7, 14 or 30).

5.2 *Test procedure:*

*5.2.1 VVM storage and handling during testing:*

- **Storage:** The VVMs and test patches must be stored below -24°C in a freezer whose temperature is recorded continuously. Testing must commence within two weeks of the arrival of the samples at the laboratory.
- **Handling:** When the samples are handled in preparation for the tests they must be removed from freezing, individually, and for the briefest period possible, before being returned again to storage below -24°C.

*5.2.2 Test conditions:*

- **Monitoring the test environment:** The temperature of the water bath and the temperature and relative humidity of the test chamber must be monitored throughout the test and a summary of the data included in the final report.
- **Temperature stability:** The temperature stability and uniformity of the water bath and of the test chamber must be controlled within a tolerance of ±0.2°C and the relative humidity must be controlled within a tolerance of ±5% RH.
- **Humidity:** Humidity in the test chamber must be controlled accurately with salt solutions, e.g., 33% RH - 370 g of Magnesium Chloride hexahydrate per 100 g of de-ionized water and 75% RH - 45 g of Sodium Chloride per 100 g of de-ionized water.

*5.2.3 Colour measurements:* Colour Measurements must be made with a Spectraflash SF600 Spectrophotometer or equivalent and with a colour reflection densitometer X-Rrite Model 404 GS or GSX (or later qualified model) or equivalent with the visual colour filter, or as agreed with the manufacturers of the VVMs.

*5.2.4 Reaction rates:* Reaction rates are specific to four different categories of VVM, relating to four groups of vaccines according to their heat stability at two specific temperature points (See Table 1).

**Table 1: VVM reaction rates by category of heat stability and temperature and time periods for testing.**

| Category (Vaccines) | No. of days to end point at +37°C | No. of days to end point at +25°C | Time to end point at +5°C |
|---|---|---|---|
| **VVM 30:** High Stability | 30 | 193 | > 4 years |
| **VVM 14:** Medium Stability | 14 | 90 | > 3 years |
| **VVM 7:** Moderate Stability | 7 | 45 | > 2 years |
| **VVM 2:** Least Stable | 2 | N/A* | 225 days |

**VVM (Arrhenius) reaction rates determined at two temperature points*

Unless otherwise specified, the two temperatures and time periods, highlighted in Table 1 for each VVM category, will be the agreed test period for testing each category. Additionally, each VVM category will be tested at a time greater than the end point time to verify that all VVM samples will reach the end point.

5.2.5 *Test 1: Format and dimensions of VVMs:* Check the dimensions of the VVMs against the limits set out in specification **E06/IN05.1**, clause 4.2.1.
The following procedure must be adopted:

- **Measurement:** For each VVM category to be tested, a random sample of 20 VVMs of each category must be used to check the ratio of the square area to the reference circle area.
- **Sample handling:** When the samples are handled for measurement, they must be individually removed from freezing, for the briefest possible period, before being returned again to storage below -2024°C.

5.2.6 *Test 2: Characterizing the colour change over time:* (Note required only one time for the product family) Specification **E06/IN05.1**, clause 4.2.2, requires a shade change without a hue change. It is therefore essential to study the colour change using both a densitometer and a spectrophotometer to ensure that the extent of hue change is small enough not significantly to affect the validity of the colour densitometer readings, which are used for the remainder of the tests.
The following procedure must be adopted:

- **Incubation:** Incubate three test patches for each VVM category to be tested. The incubation procedure must be carried out at +37°C ±0.2°C inside sealed pouches (5-mil heat sealable foil polyethylene polyesterMIL-B-131,Class 1 Type 1) or equivalent, pouches measuring 150mm x 200mm) in a water bath.
- **Readings:** Readings must be taken at time zero, and at the same time each day, until the end point is reached. Remove the sealed pouch(es) from the water bath and extract the test patch samples immediately before taking the readings.
  Each reading must consist of one measurement taken with the spectrophotometer, and one measurement taken with the colour reflection densitometer, positioning the instrument heads at the centre of the test patch.
  All readings must be taken at room temperature, in the shortest possible

time. Afterwards, the test patches must immediately be placed back into the sealed pouch(es) and returned to the water bath.
The readings must be taken for each of the three samples in each VVM category.

- **Tabulation:** The densitometer readings must be tabulated alongside the spectrophotometer readings. The difference in L value between the start point and that measured on each day of the test must be plotted against the corresponding change in optical density. If these data do not correlate, then the results must be discussed with WHO before proceeding with the remaining tests.

*5.2.7 Test 3: Recording the start point:*

- **Sample size:** 500 for each VVM category.
- **Initial procedure:**
  - Using a colour reflection densitometer, read and record the same portion of the active surface on all 20 VVM samples.
  - Take five of the samples in each category, read and record three different portions of the reference surface, and calculate the average reading for each sample. Read and record the active surface.
  - Tabulate the readings.
- **Rejection/acceptance criteria:** If the following conditions are met the next stage of the test may proceed. If one or more of the conditions are *not* met the manufacturer must be asked to submit a new batch of sample VVMs for testing.
  - The active surface readings for all each of the 20 samples must be within ±0.03 OD of the mean for the whole group.
  - When five samples are selected at random, the difference between the readings for the active surface and for the reference surface must conform to the specification for the start point set out in **E06/IN05.1**, clause 4.2.4.
  - The difference between the readings of the active surface and the reference surface (Start R-I) should conform to the specification for the start point set out in **E06/IN05.1**, clause 4.2.4.when five samples are selected at random.
  - The Indicator OD measurements at the start point should conform to the specification set out in **E06/IN05.1**, clause 4.2.4.when five samples are selected at random.
  - The three readings taken from the reference circle on five samples should conform to the specification for homogeneity set out in **E06/IN05.1**, clause 4.2.5.
  - The colour density of one portion of the reference ring compared to the colour portion of the reference ring when five samples are selected at random should conform to the variation of the reference surface specification set out in **E06/IN05.1**, clause 4.2.6.
  - The Reference Ring OD measurements at the start point should conform to the specification set out in **E06/IN05.1**, clause 4.2.7 when five samples are selected at random.
  - The specification for the Start R-I and the Indicator OD values, the Reference Ring Specification and OD limits found in E06/IN05 are based on measurements with a X-rite Model 404 GS or GSX colour reflection densitometer calibrated to the standard TEMPTIME colour

reflection reference card or to a secondary card calibrated to the TEMPTIME card. Measurements taken with other instrumentation or a X-Rite Model 404 GS or GSX colour reference densitometer calibrated to an X-Rite colour reflection reference card will require a conversion factor.

- The three readings taken from the reference circle on five samples must conform to the specification for homogeneity set out in **E06/IN05.1**, clause 4.2.5.
- If all the above conditions *are* met, the samples should be divided into four sets (I, II, III, and IV) of 60 samples each for the reaction rate tests described in clauses 5.2.8 through 5.2.12. The remainder of the samples will be used as described in clauses 5.2.13 through 5.2.15. All samples must be stored below -2024°C until testing begins.

*5.2.8 Test 4: VVM reaction rate; +37°C, no light: (applies to all VVM categories):*

- **Step 1:** Expose sample set 'I' (60 samples) to +37°C ±0.2°C inside sealed foil polyethylene MIL-B-131,Class 1 Type 1) or equivalent, pouches in a water bath, without light. Remove the relevant sealed pouch(es) from the water bath and extract the test patch samples immediately before taking the readings referred to below.
- **Step 2:** After 75% of the agreed test period in the water bath, remove the first portion (20 VVMs) from the bath. Using a colour reflection densitometer, read the active surface on all 20 samples, and record the results. Afterwards, the test patches must immediately be placed back into the sealed pouch(es) and returned to the water bath.
- **Step 3:** After completion of the agreed test period, remove the second portion (20 VVMs) from the bath. Using a colour reflection densitometer, read the active surface on all 20 samples, and record the results. Afterwards, the test patches must immediately be placed back into the sealed pouch(es) and returned to the water bath.
- **Step 4:** After 125% of the agreed test period in the water bath, remove the third portion (20 VVMs) from the bath. Using a colour reflection densitometer, read the active surface on all 20 samples, and record the results. Afterwards, the test patches must immediately be placed back into the sealed pouch(es) and returned to the water bath.
- **Step 5, for checking purposes:** Following steps 1 to 4, continue to store the set 'I' samples at +37°C for an additional 30 days. Using a colour reflection densitometer, re-read the active surface on all samples, and compare the results with those taken at the end of Step 4. Record the results of the comparison.

*5.2.9 Test 5: VVM reaction rate; +37°C, 75% RH, no light: (applies to all VVM categories)*

- **Step 1:** Expose sample set 'II' (60 samples) to +37°C ±0.2°C in a temperature-controlled cabinet, without light and at a relative humidity of 75% ±5%.
- **Step 2:** After 75% of the agreed test period in the cabinet, remove the first portion (20 VVMs) from the cabinet. Using a colour reflection densitometer, read the active surface on all 20 samples, and record the results.
- **Step 3:** After completion of the agreed test period, remove the second portion (20 VVMs) from the cabinet. Using a colour reflection

densitometer, read the active surface on all 20 samples, and record the results.

- **Step 4:** After 125% of the agreed test period in the cabinet, remove the third portion (20 VVMs) from the cabinet. Using a colour reflection densitometer, read the active surface on all 20 samples, and record the results.

5.2.10 *Test 6: VVM reaction rate; +37°C, 33% RH, no light: (applies to all VVM categories)*

- **Step 1:** Expose sample set 'III' (60 samples) to +37°C ±0.2°C in a temperature-controlled cabinet, without light and at a relative humidity of 33% ±5%.
- **Step 2:** After 75% of the agreed test period in the cabinet, remove the first portion (20 VVMs) from the cabinet. Using a colour reflection densitometer, read the active surface on all 20 samples, and record the results.
- **Step 3:** After completion of the agreed test period, remove the second portion (20 VVMs) from the cabinet. Using a colour reflection densitometer, read the active surface on all 20 samples, and record the results.
- **Step 4:** After 125% of the agreed test period in the cabinet, remove the third portion (20 VVMs) from the cabinet. Using a colour reflection densitometer, read the active surface on all 20 samples, and record the results. Move these samples to 5°C storage (see Reversion Test, clause XX5.2.13).

5.2.11 *Test 7: VVM reaction rate; +25°C, no light: (applies to VVM30, VVM14 and VVM7 categories only)*

- **Step 1:** Expose sample set 'IV' (60 samples) to +25°C ±0.2°C inside sealed foil polyethylene MIL-B-131,Class 1 Type 1) or equivalent, pouches in a water bath, without light. Remove the relevant sealed pouch(es) from the water bath and extract the test patch samples immediately before taking the readings referred to below.
- **Step 2:** After 60% of the agreed test period in the water bath, remove the first portion (20 VVMs) from the bath. Using a colour reflection densitometer, read the active surface on all 20 samples, and record the results.
- **Step 3:** After completion of the agreed test period, remove the second portion (20 VVMs) from the bath. Using a colour reflection densitometer, read the active surface on all 20 samples, and record the results.
- **Step 4:** After 140% of the agreed test period in the water bath, remove the third portion (20 VVMs) from the bath. Using a colour reflection densitometer, read the active surface on all 20 samples, and record the results.

5.2.12 *Test 8: VVM reaction rate; +5°C, no light: (applies to VVM2 category only)*

- **Step 1:** Expose sample set 'IV' (60 samples) to +5°C ±0.2°C inside sealed foil polyethylene MIL-B-131,Class 1 Type 1) or equivalent pouches in a water bath, without light. Remove the relevant sealed pouch(es) from the water bath and extract the test patch samples immediately before taking the readings referred to below.

- **Step 2:** After 60% of the agreed test period in the water bath, remove the first portion (20 VVMs) from the bath. Using a colour reflection densitometer, read the active surface on all 20 samples, and record the results.
- **Step 3:** After completion of the agreed test period, remove the second portion (20 VVMs) from the bath. Using a colour reflection densitometer, read the active surface on all 20 samples, and record the results.
- **Step 4:** After 140% of the agreed test period in the water bath, remove the third portion (20 VVMs) from the bath. Using a colour reflection densitometer, read the active surface on all 20 samples, and record the results.

*5.2.13 Test 9: Reversion test: (applies to all VVM categories)*

- **Step 1:** Following on from 5.2.2 10 Step 4, store the third portion of 20 samples from set 'III' at +5 ±0.2°C °C for 30 days.
- **Step 2:** Re-read the active surface of the samples with a colour densitometer and compare the readings with those taken at the end of the first test.

*5.2.14 Test 10: Soak test: (applies to all VVM categories)*

- **Step 1:** Adhere two groups of 10 VVM labels to water impermeable substrates (e.g., white plastic picnic plates).
- **Step 2:** Submerge the first group in a water bath at +5±0.2°C °C for 8 hours. Seal the second (dry) group of labels in foil polyethylene MIL-B-131,Class 1 Type 1) or equivalent waterproof pouches and subject to the same temperature treatment.
- **Step 3:** At the end of the 8-hour period, remove the labels from the water bath and carefully dry the soaked labels with absorbent towels.
- **Step 4:** Place both groups in a desiccant chamber at +5 ±0.2°C for 16 hours.
- **Step 5:** Remove both groups from the desiccant chamber and place in two foil polyethylene MIL-B-131, Class 1 Type 1) or equivalent waterproof pouches in a +37 ±0.2°C water bath. Once a day, remove the labels from the water bath and measure the active portion of each VVM until it reaches the end point.
- **Step 6 – evaluation:** The results of the soaked versus dry OD measurements should be compared for conformity to **E06/IN05.1**, clause 4.2.4 (less than a 0.04 OD unit difference).

*5.2.15 Test 11: Observer perception test: (applies to all VVM categories)*

- **Step 1:** Attach 15 VVM samples to empty 2 ml vials. Five of the VVM samples should be at the start point, five should be conditioned to 50% of the colour change to end point and five should be at the end point.
- **Step 2:** Place the samples in a box in a random order and store in a freezer below -24°C to prevent further colour change.
- **Step 3 – evaluation:** Five untrained observers, working independently under tungsten or fluorescent light at 100 lux on the working plane, are to sort the vaccine vials into three groups (unchanged, 50% changed, and end point). Record the level of the light used.
- **Acceptance criterion:** All five observers are able to sort the three groups of vials with 100% accuracy.

5.3 *Test criteria for qualification:*
A final report must be issued after all testing is complete. The report of the tests must contain the following data and analyses:

- **Generally:** Water bath and test chamber temperature and humidity records.
- **Test 1:** Dimensional tolerances of the VVM.
- **Test 2:** Characterization of the colour change - table of readings and plot of L vs. OD.
- **Test 3:** Distribution of active surface starting point readings - maximum, minimum and mean.
- **Test 3:** Indicator readings at the start point – table of readings.
- **Test 3:** Distribution of the difference between the active surface and the reference surface starting point readings - maximum, minimum and mean.
- **Test 3:** Homogeneity readings from the reference surface - table of readings.
- **Test 3:** Variability readings from the reference ring – table of readings.
- **Test 3:** Reference rings readings at the start point- table of readings.
- **Tests 4 to 8:** Distribution of reaction test readings at all temperatures and times - percent reaching the end point.
- **Test 9:** Reversion test.
- **Test 10:** Soak test.
- **Test 11:** Observer perception test.
- **Annexes:** Additional supporting documentation requested and received from the Legal Manufacturer or Reseller during the course of the type-testing.

**6. Quality control checklist:**

6.1 *Quality control standards:* All testing and reporting must be carried out in accordance with the requirements of ISO 17025:1999 2005 or later edition.

6.2 *Quality control checklist:* An on-site inspection of the VVM manufacturing plant is required in accordance with clause 4.

**7. Pre-qualification evaluation:**

A product will qualify for inclusion on the register of PQS pre-qualified VVMs in accordance with WHO procedures provided the final report indicates full conformity with the requirements of specification **E06/IN05.1.**

**8. Modified products:**

The legal manufacturer or reseller must notify WHO in writing of any changes which affect the performance of the product in relation to any of the requirements set out in this verification protocol. WHO will carry out a desk evaluation of the reported change(s). If any change is deemed adversely to affect the performance of the product, WHO may request full or partial re-verification based on the test procedures described in this document.

**9. Annexes:** None

| Revision history: | | | |
|---|---|---|---|
| Date | Change summary | Reason for change | Approved |
| 14 Mar 06 | Test procedure redrafted with general amendments to the form of wording but not to the content. Normative references, definitions and additional clauses added. | To achieve conformity with PQS documentation standards | UK |
| 30 Nov 06 | General revisions | Following consultation with industry | UK (30 November 2006 - PQS secretariat) |

1

## Specifications for Vaccine Vial Monitors (VVM)

- PQS Performance Specification, Vaccine Vial Monitor (WHO/PQS/E06/IN05.1)
- General Specifications for HEATmarker® Time Temperature Indicators

2

## Testing Information

- Protocol for Testing and Releasing a Lot of HEATmarker® Vaccine Vial Monitors at 37°C
- Temperature Control Requirements for VVM End-point Determination

3

## Validation Information

- Practical Validation Procedures for Vaccine Vial Monitors
- PQS Independent Type-testing Protocol, Vaccine Vial Monitor (WHO/PQS/E06/IN05.VP.1)

4

## Practical Information

- Arrhenius graphs showing temperature-dependence for each category of VVM (-30 to +50°C and 0 to 40°C)
- Instructions for Use for Vaccine Vial Monitors
- Examples of full label and dot HEATmarker VVMs
- Effect of UV/Ambient Light Exposure on Color Development of HEATmarker® Vaccine Vial Monitors

5

## Commercial Information

- 2008 World-Wide Pricing Guide and General Conditions of Sale
- Special World-Wide Pricing Guide for UNICEF Tender Contracts (2007-2009) and General Conditions of Sale

TEMPTIME

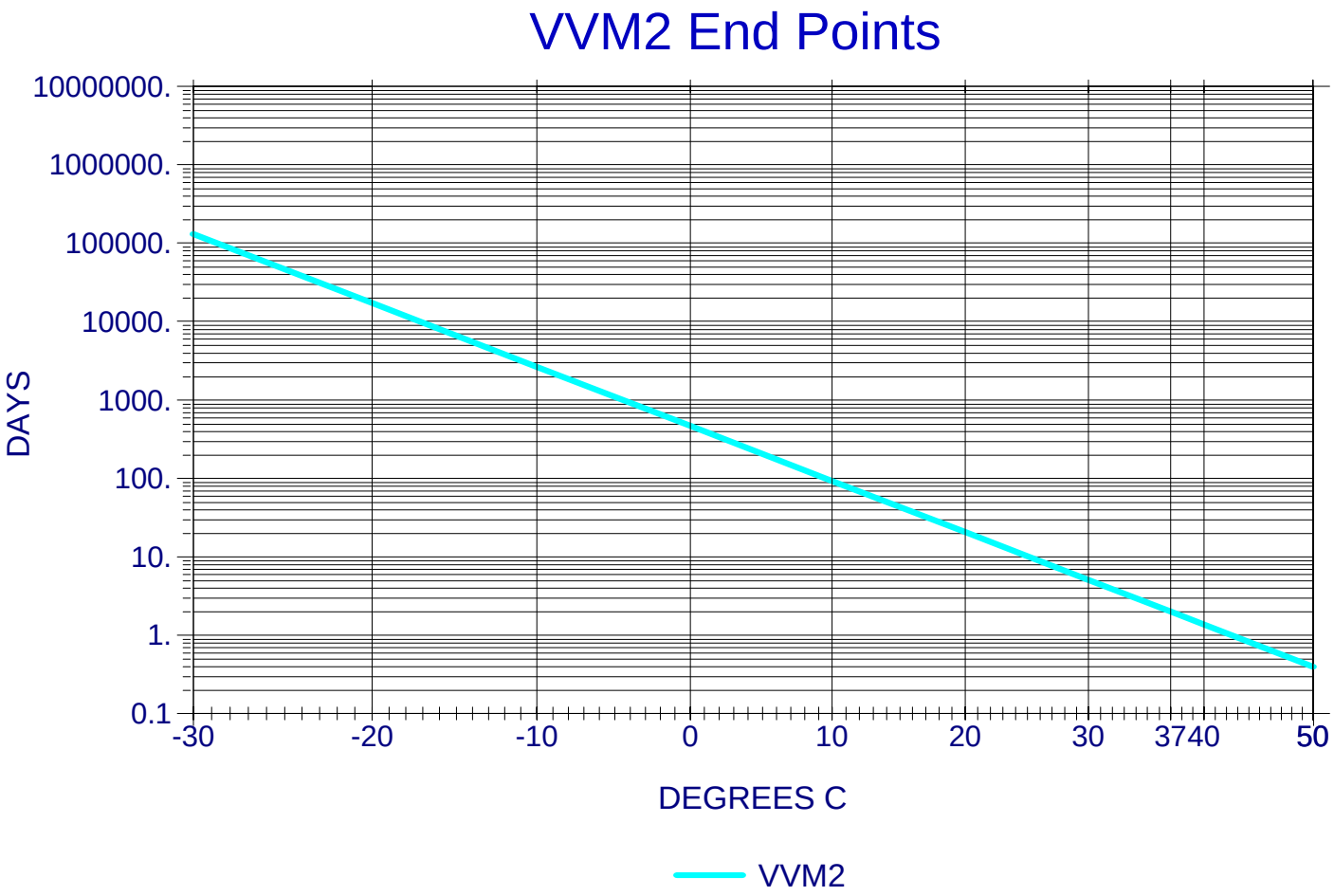
# Arrhenius Graphs showing Temperature Dependence for each Category of VVM (-30° to 50°C and 0° to 40°C)

30 March 2007

**5.1**

# Arrhenius Graphs showing Temperature Dependence for each Category of VVM (-30° to 50°C and 0° to 40°C)

4 February 2004


VVM2 End Points
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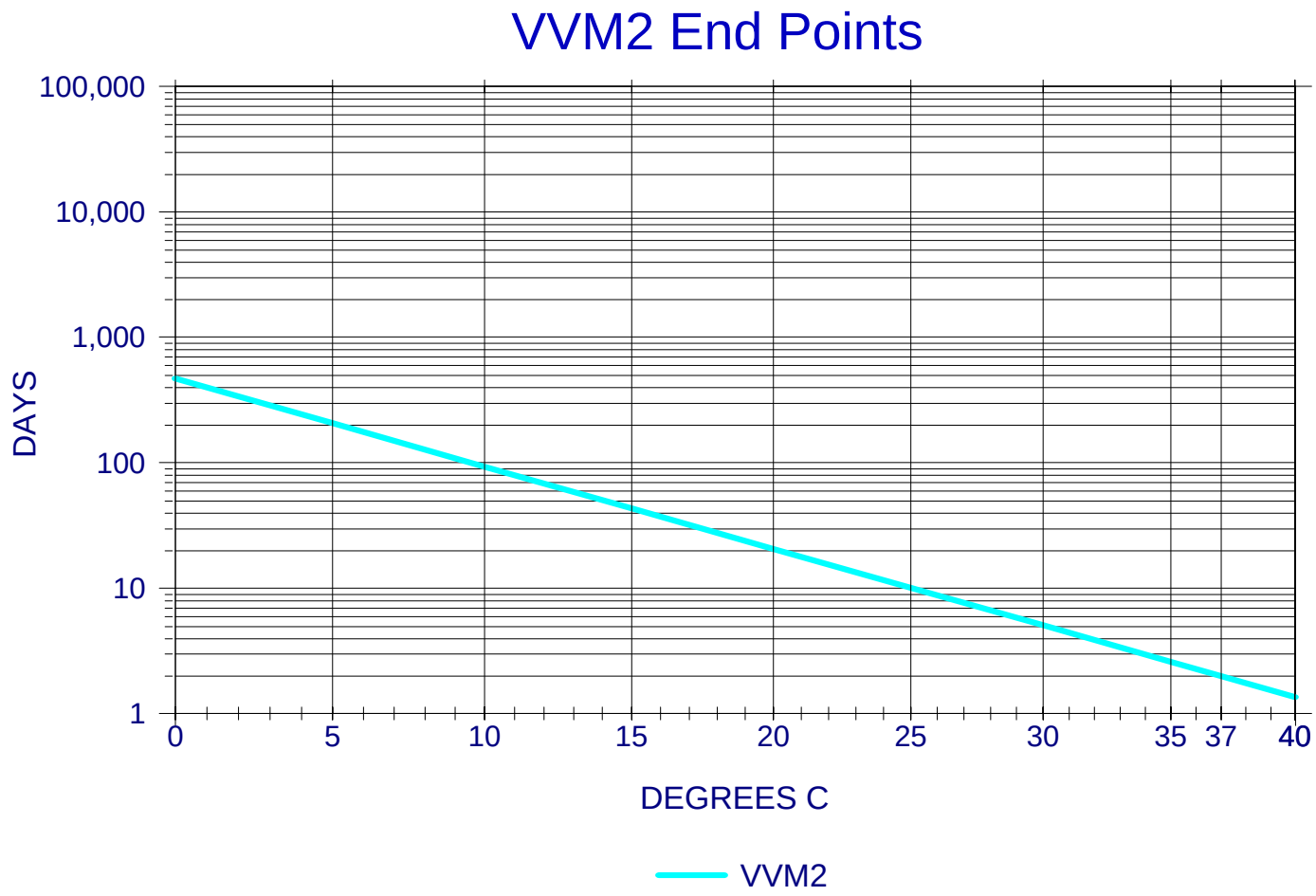
1000000.
100000.
10000.
1000.
100.
10.
1.
0.1
DAYS
-30
-20
-10
0
10
20
30
37
40
50
DEGREES C
VVM2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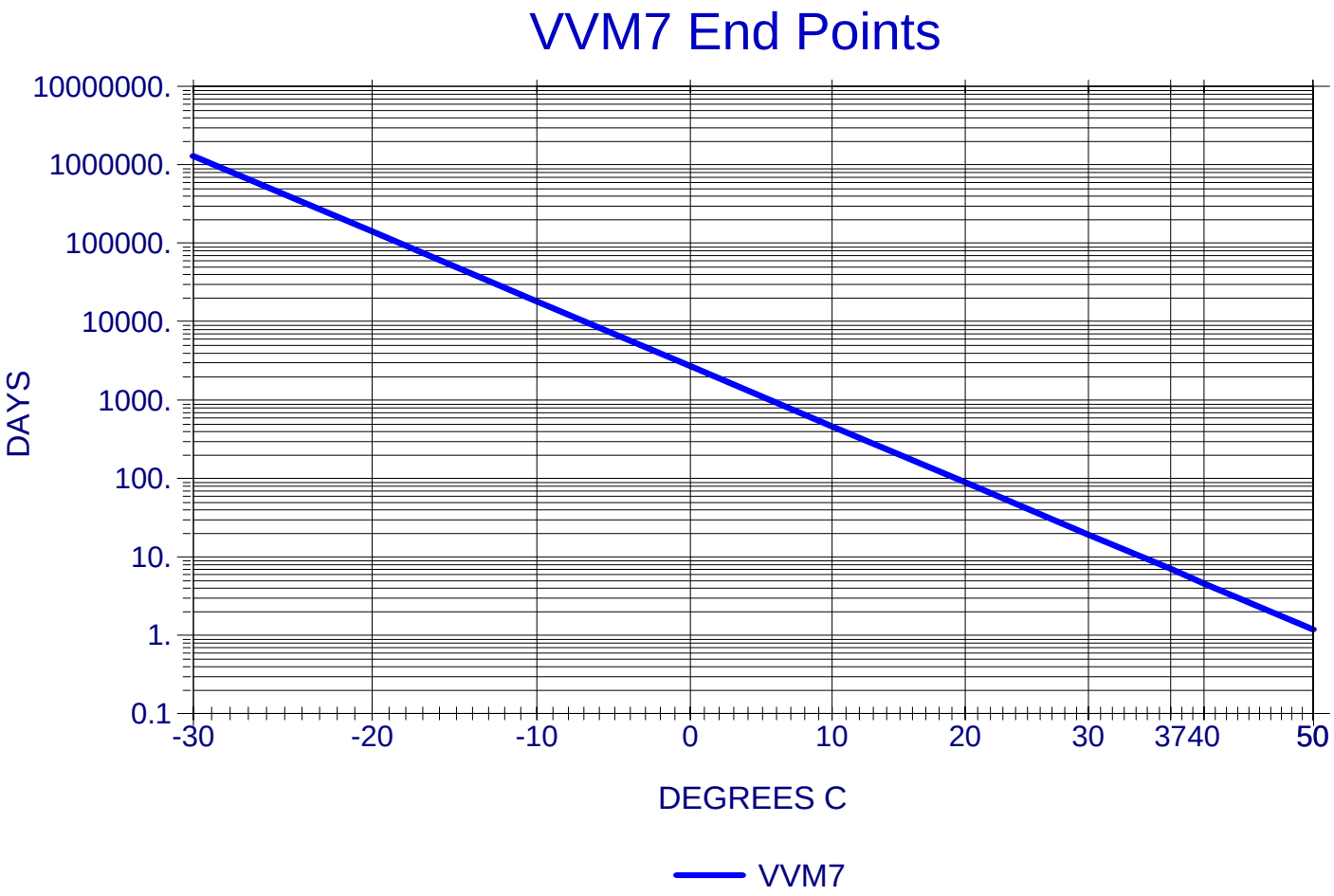
10,000
1,000
100
10
1
DAYS
0
5
10
15
20
25
30
35
37
40
DEGREES C
VVM2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100000.
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1000.
100.
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1.
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DAYS
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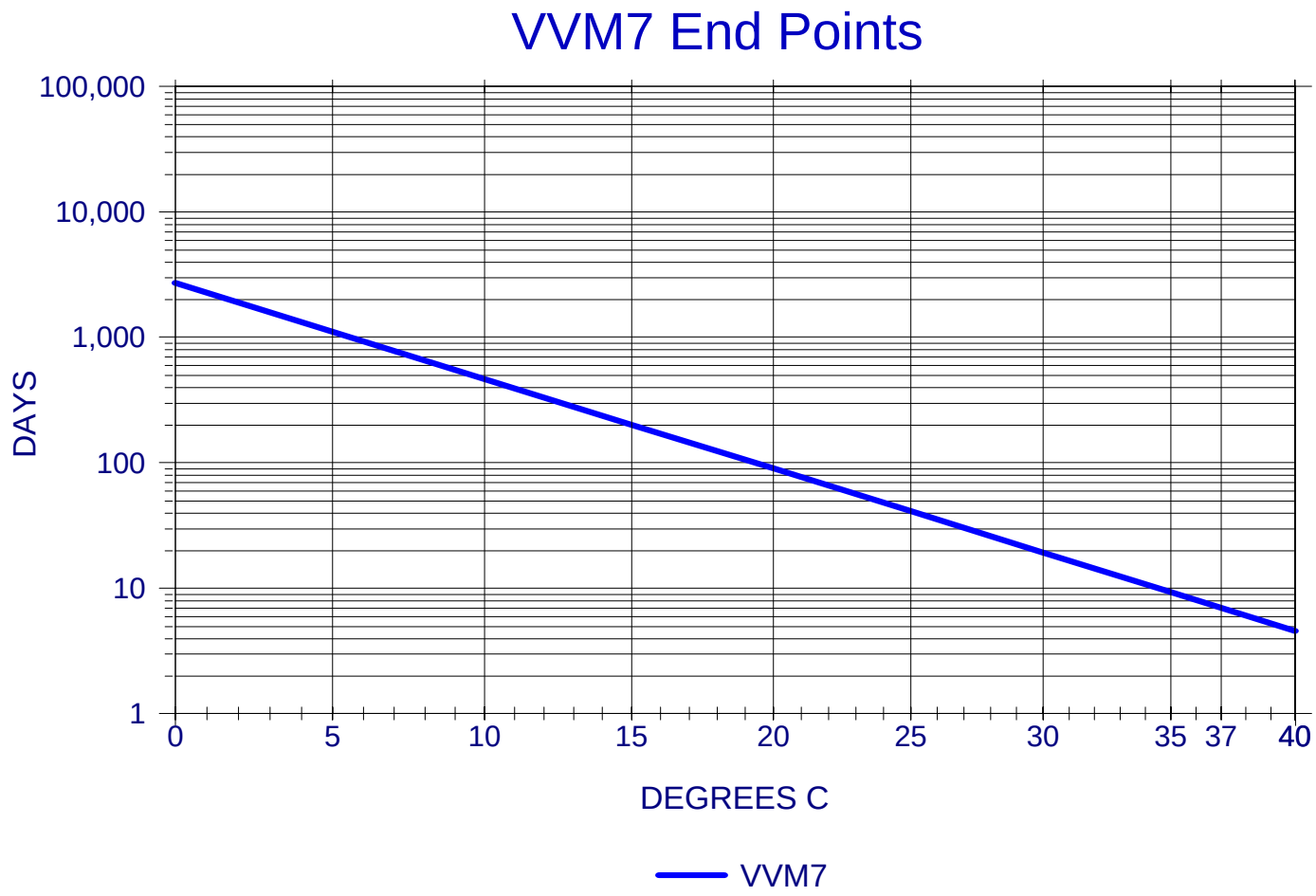
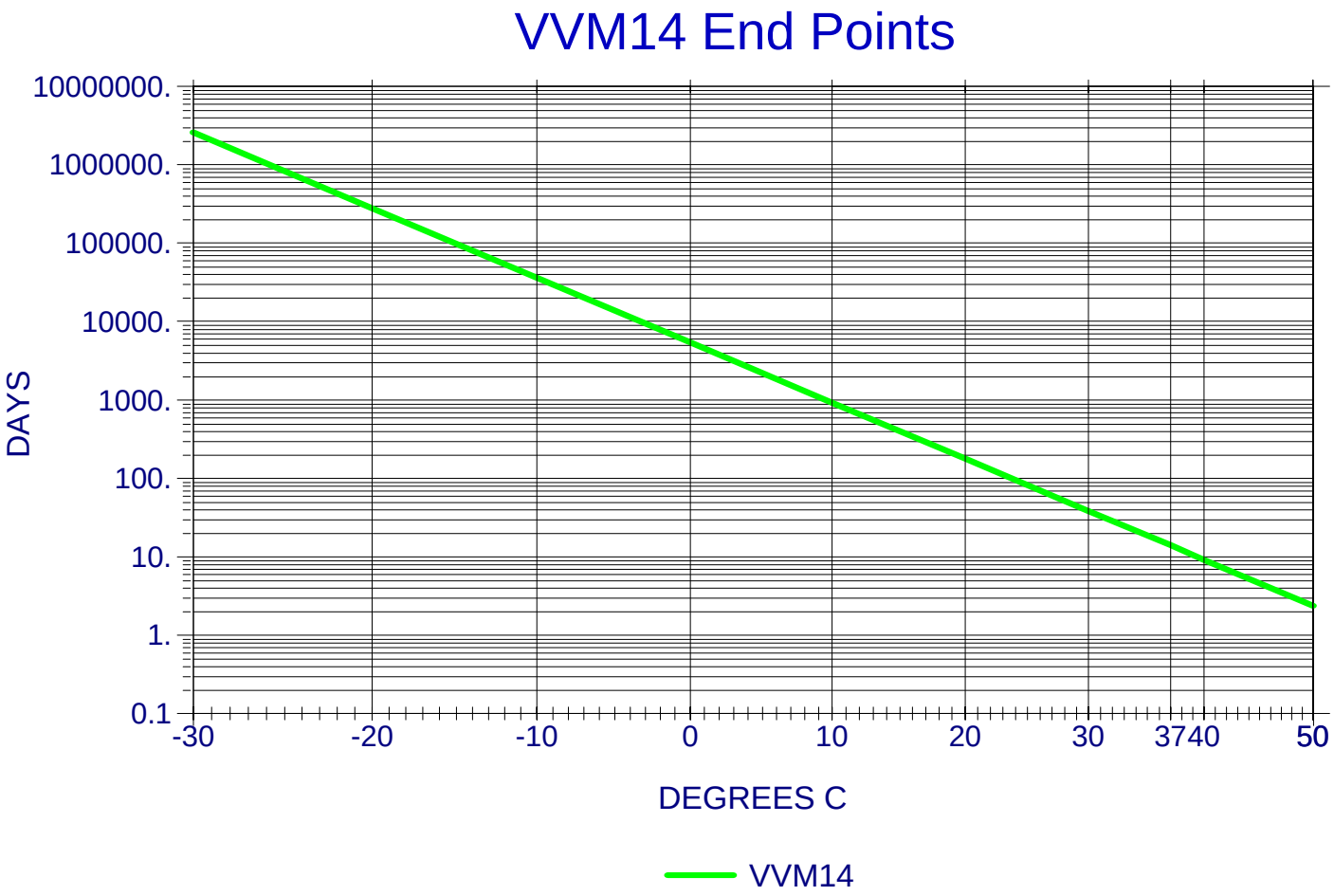
-20
-10
0
10
20
30
37
40
50
DEGREES C
VVM7


VVM7 End Points
100,000
10,000
1,000
100
10
1
DAYS
0
5
10
15
20
25
30
35
37
40
DEGREES C
VVM7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10000.
1000.
100.
10.
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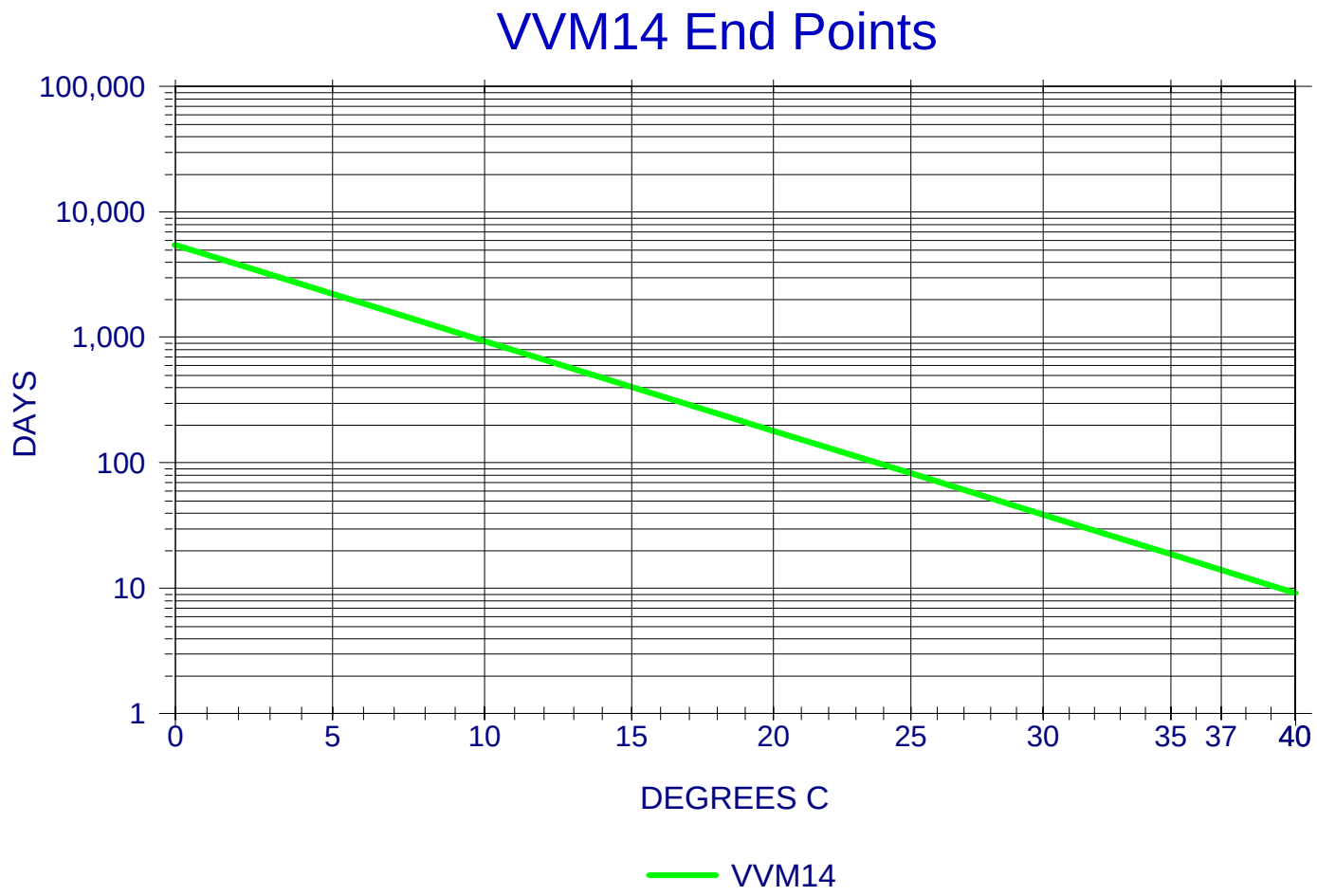
DAYS
-30
-20
-10
0
10
20
30
37
40
50
DEGREES C
VVM14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DAYS
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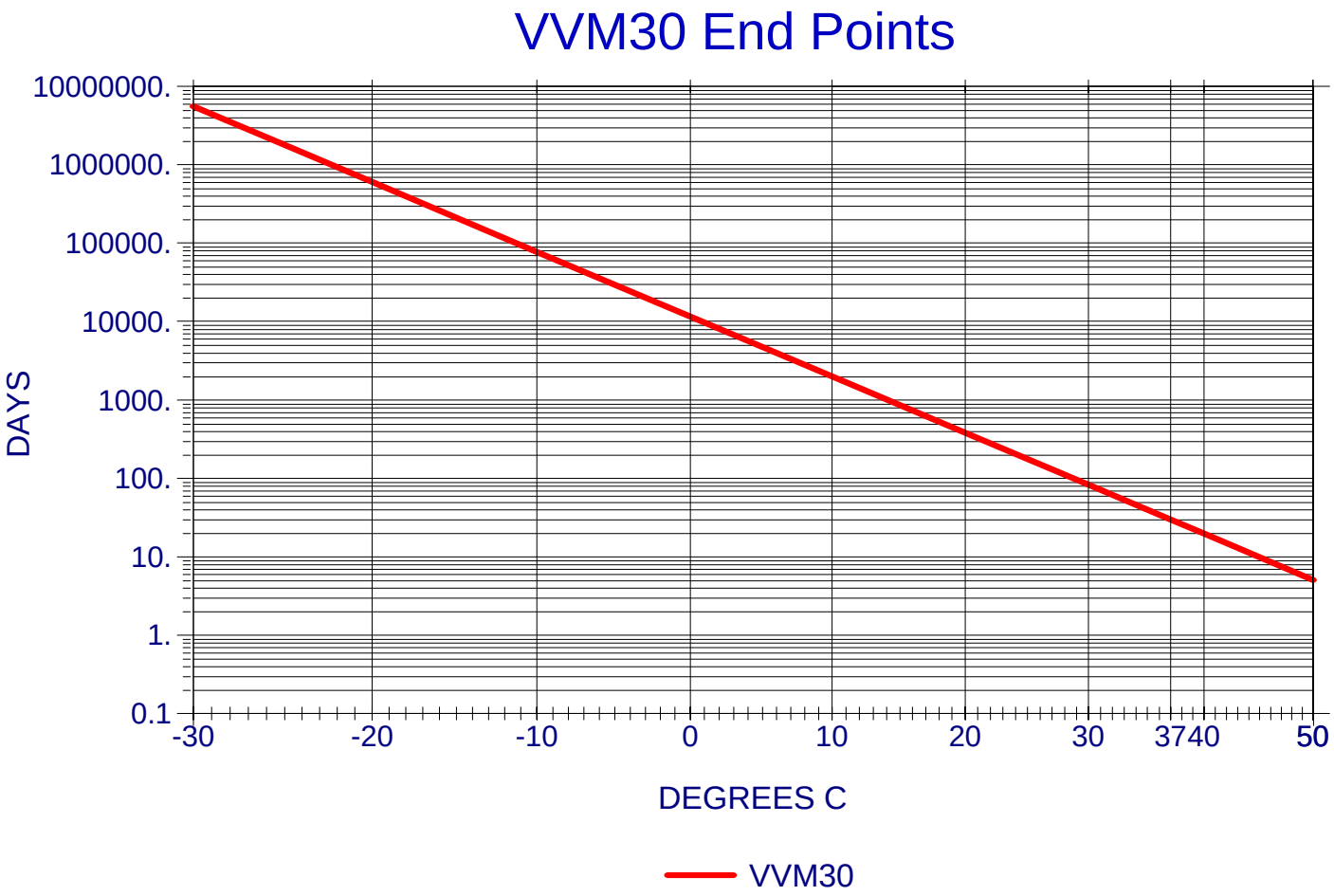
DEGREES C
VVM14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1000.
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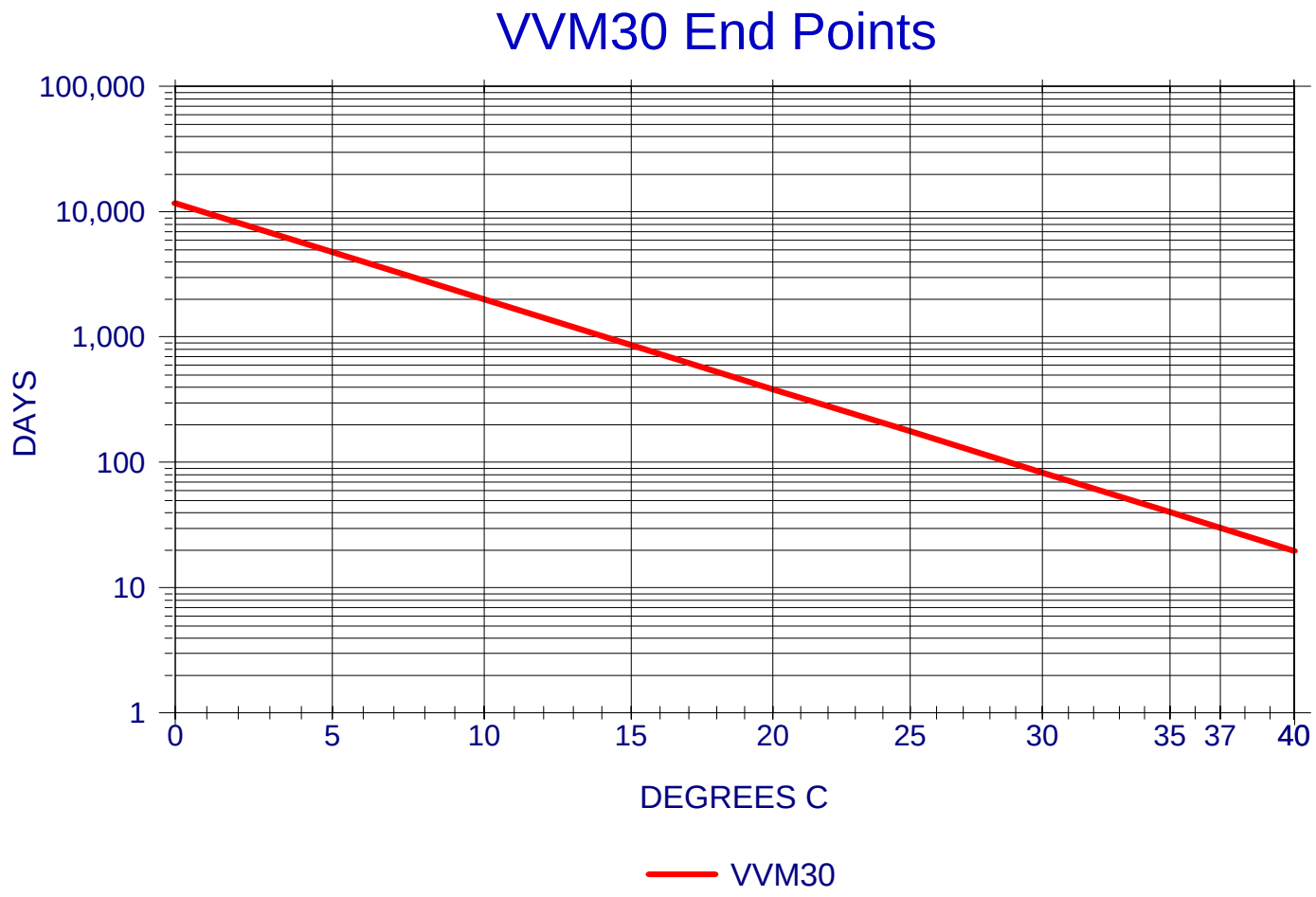
20
30
37
40
50
DEGREES C
VVM30


VVM30 End Points
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DAYS
0
5
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15
20
25
30
35
37
40
DEGREES C
VVM30

TEMPTIME

Instructions for Use

# HEATmarker® Vaccine Vial Monitors

## Description

The HEATmarker® Vaccine Vial Monitor (VVM) is a self-adhesive device that can be applied to temperature-sensitive vaccines. The VVM is a device that can monitor the temperature exposure over time for individual vials of vaccine. The VVM can be applied to primary label, the vial cap, or the neck of the ampoule. The structure of the VVM is similar to a label in that it can be permanently affixed to the vial.

The visible surface of the indicator contains an area of color-changing material (active surface) surrounded by an area of fixed color (reference surface) (see Figure 1). The VVM varies from start point (light) to end point (dark), when the inner active surface reaches the same color as the fixed reference surface.

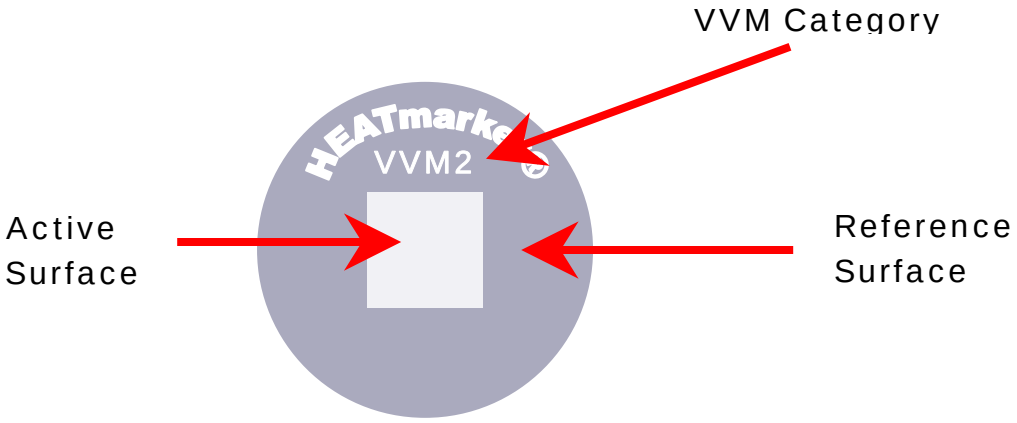



***Figure 1 – Diagram of the HEATmarker ® Vaccine Vial Monitor (VVM2 shown as an example) -*** *The combined effects of time and temperature cause a gradual, predictable, cumulative, and irreversible color change in the active surface from near colorless to black.*

HEATmarker® VVMs have been used to monitor the temperature exposure of vaccines since 1996 following the recommendation of the World Health Organization

(WHO) and UNICEF.[7] The VVM alerts the health care worker if a vial of vaccine has been damaged by heat and should not be administered.

## Intended Use

The HEATmarker® Vaccine Vial Monitor is intended to be used by a health care provider to distinguish between vaccines that have been or have not been exposed to a specific time and temperature profile of interest.

## Indications for Use

When affixed to a vaccine, the HEATmarker® Vaccine Vial Monitor (VVM) is indicated, via a permanent color change, for the purpose of distinguishing between vials of vaccine that have exceeded a selected time-temperature profile of interest to the user from vials of vaccine that have not exceeded that profile. VVMs are available in different categories based on their rate of change at specified time and temperature profiles. The user selects the appropriate VVM from among available categories, following the instructions and referring to the tables in the accompanying labeling.

## Selecting the Appropriate VVM

The selection of the proper VVM is the responsibility of the user. The following table should be used to identify the appropriate category VVM to be used. The stability of the vaccine at 37°C should be known.

| **Category: (Vaccines)** | **No. days to end point at +37°C** | **No. days to end point at +25°C** | **Time to end point at +5°C** |
|---|---|---|---|
| **VVM30** HIGH STABILITY | 30 | 193 | > 4 years |
| **VVM14** MEDIUM STABILITY | 14 | 90 | > 3 years |
| **VVM7** MODERATE STABILITY | 7 | 45 | > 2 years |
| **VVM2** LEAST STABLE | 2 | NA* | 225 days |

**VVM (Arrhenius) reaction rates determined at two temperature points*

***Table 1 –Time to endpoint for the four VVM categories at different temperatures***

Example:
A vaccine with low stability, meaning it would be damaged by exposure to a temperature of 37°C for 2 days, should use the VVM2 category.

## Storage and Application

The HEATmarker® Vaccine Vial Monitors should be stored at any temperature below -24ºC prior to use. The color-changing properties of the VVMs are also sensitive to UV light and should therefore be stored in the dark.

Once the environmentally sensitive vaccine is removed from controlled storage, the VVM should be applied. The polymerization of the active surface of the VVM is continuous and faster at higher temperatures. Avoid prolonged exposure of the VVM to elevated temperatures prior to and during application. The VVM monitors the temperature history of the vaccine from the time it is removed from cold storage until the time the product is used.

Affix the VVM to an area that does not obstruct the original manufacturer's labeling. Since the VVM is sensitive to UV light, the vial to which the VVM has been applied should be protected from sunlight and other sources of UV light.

Prior to using the vial of vaccine, verify that the TTI has not reached or exceeded the endpoint as shown below.

## How to Read the VVM

1. When the inner square (active surface) is lighter than the outer circle (reference surface), the vaccine is OK to be used (as long as it is within the manufacturer's expiration date).
2. When the inner square (active surface) has the same color as the outer circle (reference surface), endpoint has been reached; the vaccine should not be used.
3. When the inner square (active surface) is darker than the outer circle (reference surface), the endpoint has been exceeded; the vaccine should not be used.

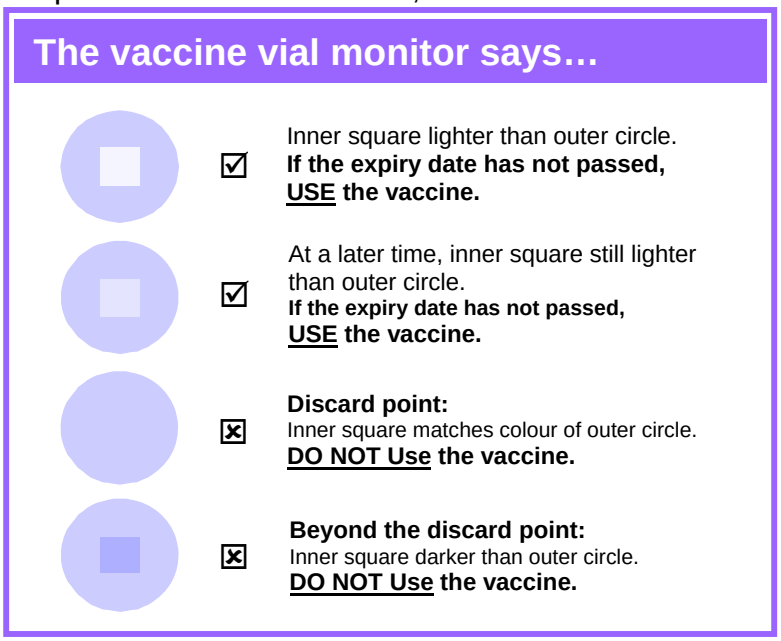



***Figure 2 – Life cycle of TEMPTIME Vaccine Vial Monitor***

## Precautions

- The HEATmarker® Vaccine Vial Monitors are sensitive to UV light.[6]
- Store unused VVMs in a dark area or in a light-protecting container or pouch at or below -24ºC.
- After application, the vial to which the VVM has been applied should be protected from exposure to sunlight or other UV light.
- The VVM is not a replacement for the manufacturer's expiration date. Do not use a vaccine that has exceeded its original expiration date even if the VVM has not reached endpoint.
- Adhesion of the VVM may be affected by affixing it to a wet and/or frozen surface. For best results, affix the VVM to a dry substrate at a temperature above 0ºC.

## Bibliography

1. Allegra, J. R., Brennan, J., Lanier, V., Lavery, R. and Mackenzie, B. "Storage Temperatures of Out-of-Hospital Medications", Academic Emergency Medicine, November 1999, pp.1098-1103.

2. Allegra, J. R., Brennan, J., Fields, L., Grabiner, F., Kiss, G., Lavery, R., and Prusik, T. "Monitoring the Storage Temperature of Ambulance Medications with Time-Temperature Indicators". Hospital Pharmacy. Volume 35, March 2000. pp. 246-250.

3. United States Pharmacopeia, General Chapter <1118> Monitoring Devices – Time, Temperature and Humidity.

4. United States Pharmacopeia, Proposed General Chapter <1070> Emergency Medical Services Vehicles and Ambulances – Storage of Medications.

5. United States Pharmacopeia, Proposed General Chapter <386> Environmentally Sensitive Preparations.

6. "Effect of Ambient UV Light Exposure on Color Development of HEATmarker ® Vaccine Vial Monitors (VVMs)". TEMPTIME Corporation (then known as LifeLines Technology) report dated 27 June 2003.

7. "Implementation Update on VVM (Vaccine Vial Monitor)". TEMPTIME Corporation report dated 15 April 2005.

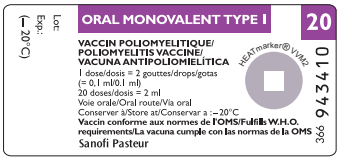
## Manufactured by:

TEMPTIME Corporation
116 American Rd.
Morris Plains, NJ 07950
Tel: (973) 984-6000
FAX: (973) 984-1520
Contact: Steve Feldman
VP Quality & Regulatory Affairs
e-mail: stevef@temptimecorp.com

# Examples of HEATmarker™ VVMs

**Full Label VVM** (common label + time-temperature indicator) - is a customized order specifically manufactured for one vaccine manufacturer, for one specific vaccine and for one specific WHO VVM category type (2 days @37°C; 7 days @37°C; 14 days @37°C and 30 Days @37°C)

## Sanofi Pasteur

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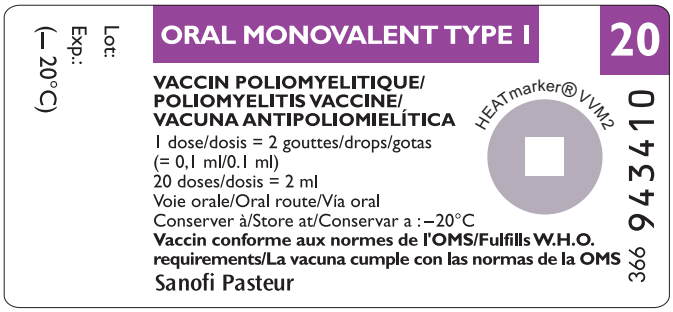
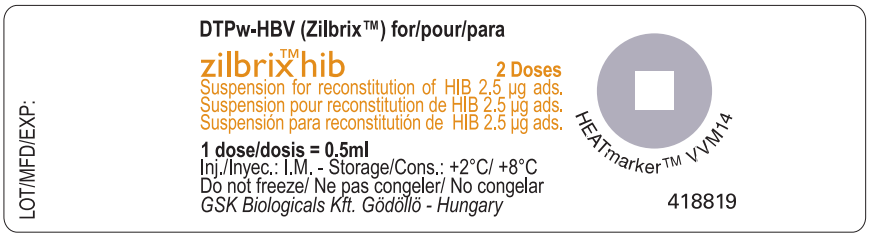



Double Size

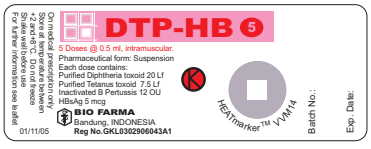
## GlaxoSmithKline


15mm X 57mm

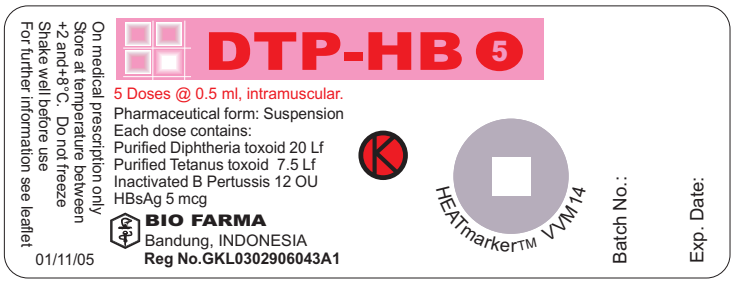



Double Size

## P.T. Bio Farma




18mm X 48mm

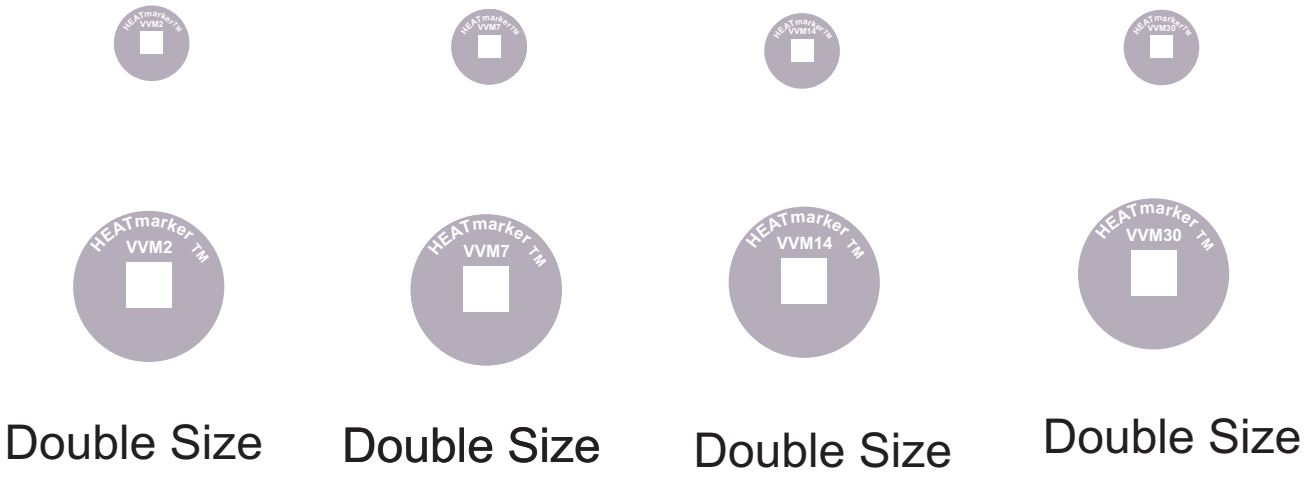



Double Size

# Examples of HEATmarker™ VVMs

**Dot VVM** (time-temperature indicator only) - is a standard time-temperature indicator without text, one standard for each specific WHO VVM category type (2 days @37°C; 7 days @37°C; 14 days @37°C and 30 Days @37°C)

## 1. Standard 10mm Dot
## VVM2, VVM7, VVM14 and VVM30

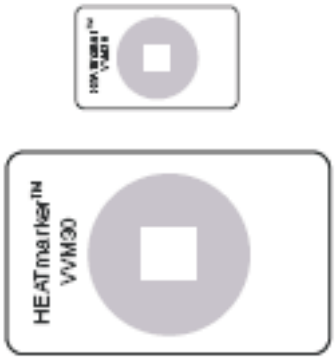



Double Size Double Size Double Size Double Size

## 2. Other Dot Presentations

### VVM14 and VVM30 - Yellow Fever and BCG Vaccine in glass ampoules

### 10mm X 16mm



TEMPTIME

# Effect of Ambient UV Light Exposure on Color Development of HEATmarker ®Vaccine Vial Monitors (VVMs)

27 June 2003

# Effect of Ambient UV Light Exposure on Color Development of HEATmarker ®Vaccine Vial Monitors (VVMs)

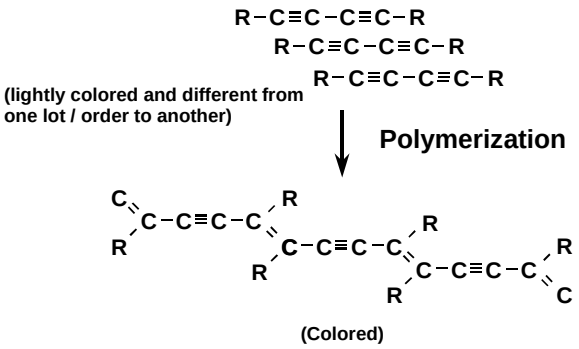
## Table of Contents

## 1. Background and Purpose

### *1.1. Background:*

The color change that takes place in the reactive square of HEATmarker VVMs is based on the solid-state polymerization reaction of proprietary, substituted diacetylene monomers. The monomers are very lightly colored once they are synthesized, and as a result of the polymerization reaction they become highly colored.

**Polymerization of Diacetylene Monomers**




As with many polymerization reactions involving molecules with conjugated triple bonds, the polymerization reaction can be accomplished as a result of time and temperature exposure, but can also be accomplished by actinic radiation in the visible but mostly UV portion of the spectrum.

### *1.2. Purpose:*

1.2.1. To quantify the impact of different sources of light encountered during handling and use of HEATmarker® VVMs on the optical density (color).

1.2.2. To recommend handling procedures to minimize these effects.

## 2. Scope

### *2.1. VVM Types*

2.1.1.1.Four types of VVMs: VVM2, VVM7, VVM14, and VVM30.

### *2.2. Light Sources*

2.2.1. Direct sunlight – outside on a sunny day

2.2.2. Indirect sunlight – outside, shade

2.2.3. Direct sunlight – inside, through a closed window. Window is lightly tinted grey, with no particular UV blocking capability.

2.2.4. Artificial lighting – inside, cool white fluorescent light

2.2.5. Artificial lighting – inside, incandescent light

2.2.6. Artificial lighting – inside, high-output fluorescent lighting in a manufacturing plant

2.2.7. Dark control (VVMs sealed in aluminum foil) exposed to same temperature and humidity conditions as 2.2.1 through 2.2.6.

### *2.3. Temperature, Humidity, Light Intensity, and Duration of Exposure*

2.3.1. Each test will be at ambient temperature and humidity
- 2.3.1.1. Temperature and humidity will be measured and recorded periodically.

2.3.2. Duration of test will simulate possible exposure under use conditions:
- 2.3.2.1. Direct and indirect sunlight
  - 2.3.2.1.1. VVM2 – 30 minutes in sun, 2 hours in shade, 2.7 hours in direct sun through window
  - 2.3.2.1.2. VVM7, VVM14, VVM30 – 2 hours in sun and in shade, 2.7 hours in direct sun through window
- 2.3.2.2. Indoor artificial lighting
  - 2.3.2.2.1. 6.9 days in high-output fluorescent light and in cool white fluorescent light
  - 2.3.2.2.2. 1.8 days in incandescent light

2.3.3. Use calibrated radiometers and light meters for light intensity measurements.

2.3.4. Use calibrated Onset HOBO data recorders[1] for light intensity, relative humidity, and temperature measurements.

### *2.4. Location and Dates of Tests*

2.4.1. Direct sunlight
- 2.4.1.1.Location – on the cement pavement with southern exposure outside TEMPTIME Corporation's entrance in Morris Plains, New Jersey.
- 2.4.1.2.Date – 7 August 2002

2.4.2. Indirect sunlight
- 2.4.2.1.Location – in the shade behind a building identification sign outside TEMPTIME Corporation's entrance in Morris Plains, New Jersey.
- 2.4.2.2.Date – 7 August 2002

2.4.3. Direct sunlight – inside, through a closed window.
- 2.4.3.1.Location – Downstairs office window at TEMPTIME Corporation in Morris Plains, New Jersey. Window has southern exposure.
- 2.4.3.2.Date – 7 August 2002

2.4.4. Artificial lighting – inside, cool white fluorescent light
- 2.4.4.1.Location – R&D laboratory #1 at TEMPTIME Corporation in Morris Plains, New Jersey on bench top
- 2.4.4.2.Date – 30 July 2002 – 6 August 2002

2.4.5. Artificial lighting – inside, incandescent light
- 2.4.5.1.Location – main telephone switching room on 2nd floor at TEMPTIME Corporation in Morris Plains, New Jersey
- 2.4.5.2.Date – 30 July 2002 – 1 August 2002

2.4.6. Artificial lighting – inside, high-output fluorescent lighting in a manufacturing plant

[1] Onset HOBO H08-004-02, capable of measuring relative humidity, light, and temperature.

2.4.6.1.Location – on a shelf in the printing room at TEMPTIME Corporation in Morris Plains, New Jersey
2.4.6.2.Date – 30 July 2002 – 6 August 2002

## 3. Materials / Equipment:

3.1. Densitometer – *X-Rite Model 404 GS*, calibrated to TEMPTIME Corporation color standard. Serial number 12394.

3.2. Radiometer - digital UVA + UVB meter. Solarmeter model 5.0 (serial number 10337) 0 – 199.9 mW/cm$^2$; response range 280 – 400 nm (UVB through UVA); resolution 0.1 mW/cm$^2$; accuracy +/- 5%; traceable to NIST standard. Solarmeter model 5.7 (serial number 10551) 0 – 1999 μW/cm$^2$; response range 280 – 400 nm (UVB through UVA); resolution 1 μW/cm$^2$; accuracy +/- 5%; traceable to NIST standard. These radiometers measure instantaneous total UVA and UVB intensity.

3.3. Photographic light meter - Gossen Luna Pro, serial number 5C50563.

3.4. HOBO loggers- Onset HOBO H08-004-02 loggers capable of measuring relative humidity, light, and temperature (Serial numbers 570874, 570876, and 570877).

3.5. VVMs (see Annex A for Certificates of Analysis for each lot)

| *VVM Type* | *Manufacture Date* | *Lot* | *Roll Number* | *Laminated with Polypropylene* |
|---|---|---|---|---|
| VVM30 | 29 April 2002 | LG119/1 | 280 | Yes |
| VVM14 | 15 May 2002 | LG135/1 | 429 | Yes |
| VVM7 | 20 June 2002 | LG171/1 | 39 | Yes |
| VVM2 | 11 April 2002 | LG101/1 | 17274 | Yes |
| VVM2 | 9 January 2002 | LG009/1 | 167 | No |

## 4. Procedure

4.1. Sample preparation

4.1.1. Remove 5 VVMs of each type from release liner and apply to white index card (see Figure 4.1.1 below).

4.1.2. Identify card for VVM type and test condition.

4.1.3. Repeat for each test condition and dark control.

**Figure 4.1.1 – VVMs attached to white card**


*Figure 4.1.1 shows the five VVMs of each type attached to the white card at the beginning of the test.*

4.2. Time zero (baseline) color reading

4.2.1. Using program XRQ[2], measure indicator and reference of each VVM (2 times) using a calibrated X-Rite 404 densitometer in cyan mode. Use XRIN[3] program for data capture. XRIN averages the measurements from the 5 VVMs.

4.3. Sample storage prior to start of test

4.3.1. Place samples, protected from light, in a freezer capable of maintaining temperature of <-24°C before initiation of test.

4.4. Sample placement and measurement of temperature, humidity and light intensity

4.4.1. Place sample in test condition. Record date and time.

4.4.2. Position dark control next to sample.

4.4.3. Position radiometer and light meter next to sample.

4.4.3.1. Record readings.

4.4.3.2. Measure distance from samples to light source.

4.4.4. Position HOBO logger next to sample (logger previously programmed to measure temperature, humidity and light every 6 minutes for tests conducted in artificial lighting, and every 2 minutes for the sunlight tests).

[2] XRQ is a TEMPTIME Corporation, Inc PC program used to transfer data from a densitometer to a PC data file.
[3] XRIN is a TEMPTIME Corporation, Inc spreadsheet macro program used to import the data file into a spreadsheet and prepare summaries and graphs.

4.5. Measurement of samples in test conditions

4.5.1. Measure the reference ring and indicator of the test and control VVMs at the following intervals:

4.5.2. Sunlight tests

4.5.2.1. Direct sun

| VVM2 | VVM7 | VVM14 | VVM30 |
|---|---|---|---|
| 10 min | 10 min | | |
| 20 min | 20 min | 20 min | |
| 30 min | 30 min | 30 min | 30 min |
| | 60 min | 60 min | 60 min |
| | 120 min | 120 min | 120 min |

4.5.2.2. Shade

| VVM2 | VVM7 | VVM14 | VVM30 |
|---|---|---|---|
| 10 min | 10 min | | |
| 20 min | 20 min | 20 min | |
| 30 min | 30 min | 30 min | 30 min |
| 60 min | 60 min | 60 min | 60 min |
| 120 min | 120 min | 120 min | 120 min |

4.5.2.3.Direct sun through a closed window

| VVM2 | VVM7 | VVM14 | VVM30 |
|---|---|---|---|
| 18 min | 18 min | | |
| 43 min | 43 min | 43 min | |
| 79 min | 79 min | 79 min | 79 min |
| 162 min | 162 min | 162 min | 162 min |

4.5.3. Artificial light tests

4.5.3.1. High-output fluorescent lighting in the manufacturing plant: 6.7 hours, 21.1 hours, 43.6 hours, 6.9 days

4.5.3.2. Cool white fluorescent: 7.3 hours, 21.6 hours, 44.0 hours, 6.9 days

4.5.3.3. Incandescent light: 7.1 hours, 21.4 hours, 44.4 hours

4.6. Record the light intensity measured by the Solarmeter and photographic light meter each time the sample is taken out of the test condition for color measurement.

4.7. Download HOBO loggers after completion of each test.

4.7.1. HOBO loggers remain in test conditions as samples are pulled for measurements. Measurement of OD takes between 15 to 20 minutes for the test set and control set. For the outside light tests, the shade and sun samples and corresponding controls are removed for measurement at the same time, so measurement of OD takes between 30 and 40 minutes. For this reason, the duration time indicated in the temperature, humidity, and light intensity graphs from the HOBO data logger will be longer than the actual exposure time.

## 5. Summaries:

### 5.1. Summary of Test Conditions

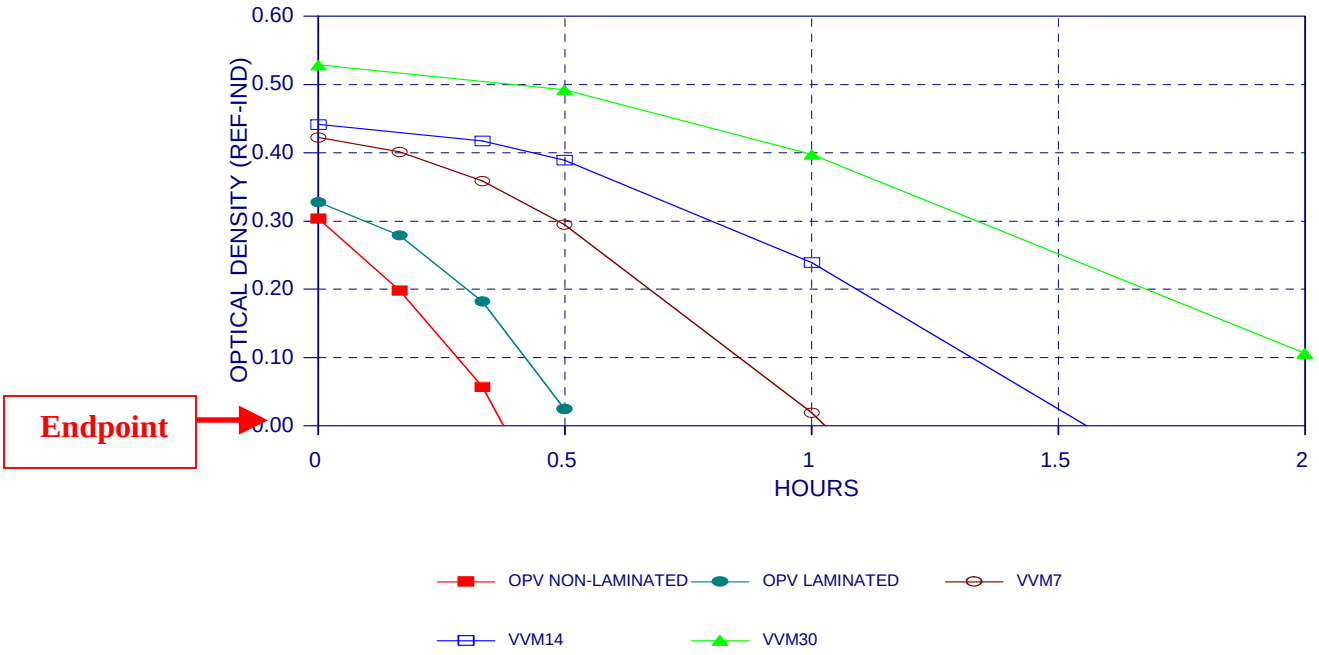
The following table summarizes the characteristics of the different test conditions.

| *Summary of Duration, Temperature, Humidity, and Light of Each Test Condition* | | | | | | |
|---|---|---|---|---|---|---|
| **Location** | **Duration of test** | **Ave Temp (˚C)** | **Ave. Humidity (%RH)** | **UVA+UVB Radiometer ($\mu W/cm^2$)** | **White light HOBO logger ($Lumen/ft^2$)** | **White Light Photograhic Light Meter (Lux = $Lumen/M^2$)** |
| Direct sun | 2 hours | 42.0 | 28.4 | 3,100 – 5,200 | > 600 (exceeds range) | 131,500 - 350,000 |
| Shade | 2 hours | 26.3 | 35.4 | 200 – 500 | > 600 (exceeds range) | 4,150 – 44,000 |
| Direct Sun Through Window | 2.7 hours | 29.0 | 27.0 | 300 – 1,700 | > 600 (exceeds range) | 5,500 – 22,000 |
| Fluorescent Light - Lab | 6.9 days | 23.3 | 54.9 | < 1 | 74.0 | 350 |
| Fluorescent light - plant | 6.9 days | 22.0 | 62.3 | 9 | 55.8 | 350 |
| Incandescent light | 1.8 days | 31.7 | 26.4 | 2 | 211 | 700 |

### 5.2. Summary of the results of each type of light exposure on each type of VVM

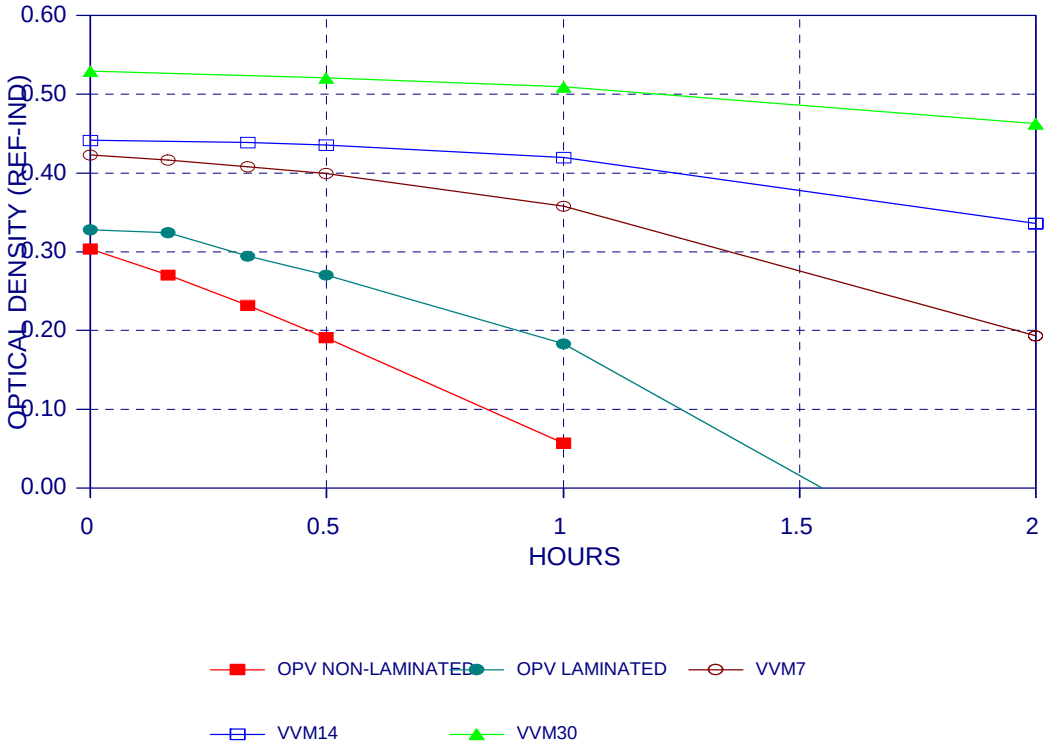
The optical density in all figures is reported as the difference between the reference ring and the indicator. As the indicator gets darker, the difference in optical density shown in the graph gets smaller. The endpoint of the indicator is when the difference between the reference ring and indicator equals 0.00. The difference in start OD of each VVM type is typical: start OD approximately 0.30 for VVM2, 0.40 for VVM7 and VVM14, 0.50 for VVM30.

**Figure 5.2.1**
**Effect of direct sunlight on VVM color development**




As expected, direct sunlight has a very important impact on the all the VVMs as shown in Figure 5.2.1. VVM2 without lamination reaches the endpoint in about 25 minutes. VVM2 with lamination reaches the endpoint in just over 30 minutes. VVM7 takes about 1 hour to reach the endpoint, while VVM14 takes over 1.5 hours. The sensitivity of the VVMs to direct sunlight follows the same trend as the thermal sensitivity: VVM2 > VVM7 > VVM14 > VVM30. These results show that all VVMs must be protected from direct sunlight.

**Figure 5.2.2**
**Effect of indirect sunlight on VVM color development**

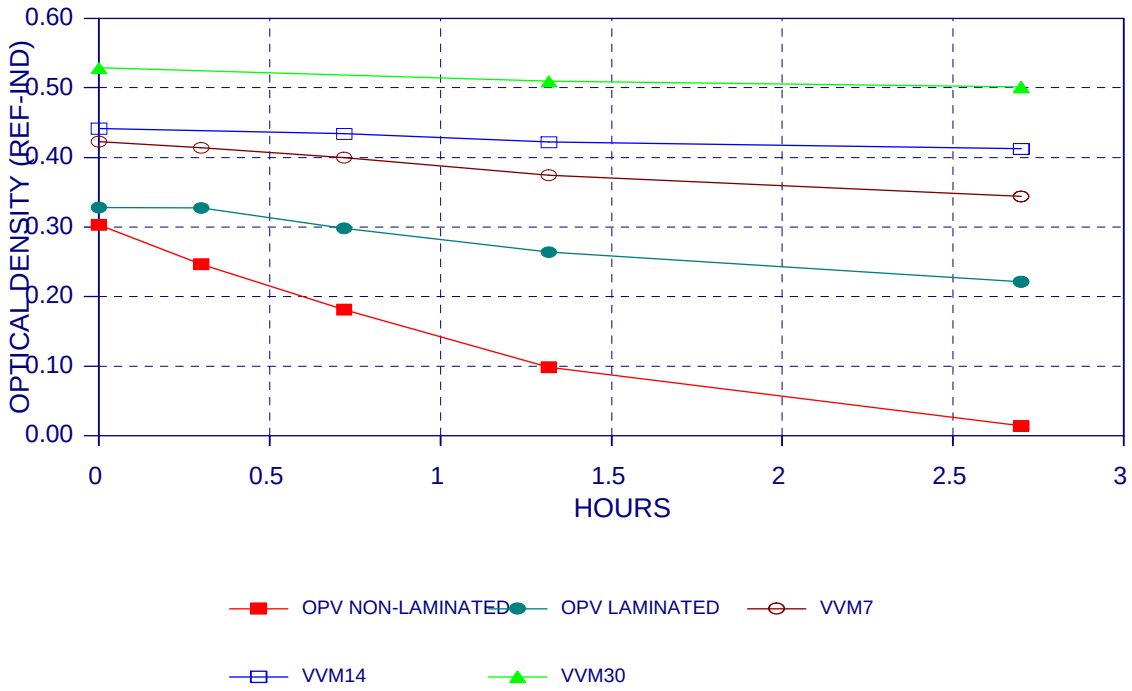



Indirect sunlight (shade) has a very significant impact on all the VVMs as shown in Figure 5.2.2. The impact is about four to six times less after 30 minutes exposure when compared with the direct sunlight results. Unlaminated VVM2 reaches the endpoint in about 1.1 hours, while laminated VVM2 takes just over 1.5 hours.

# Figure 5.2.3

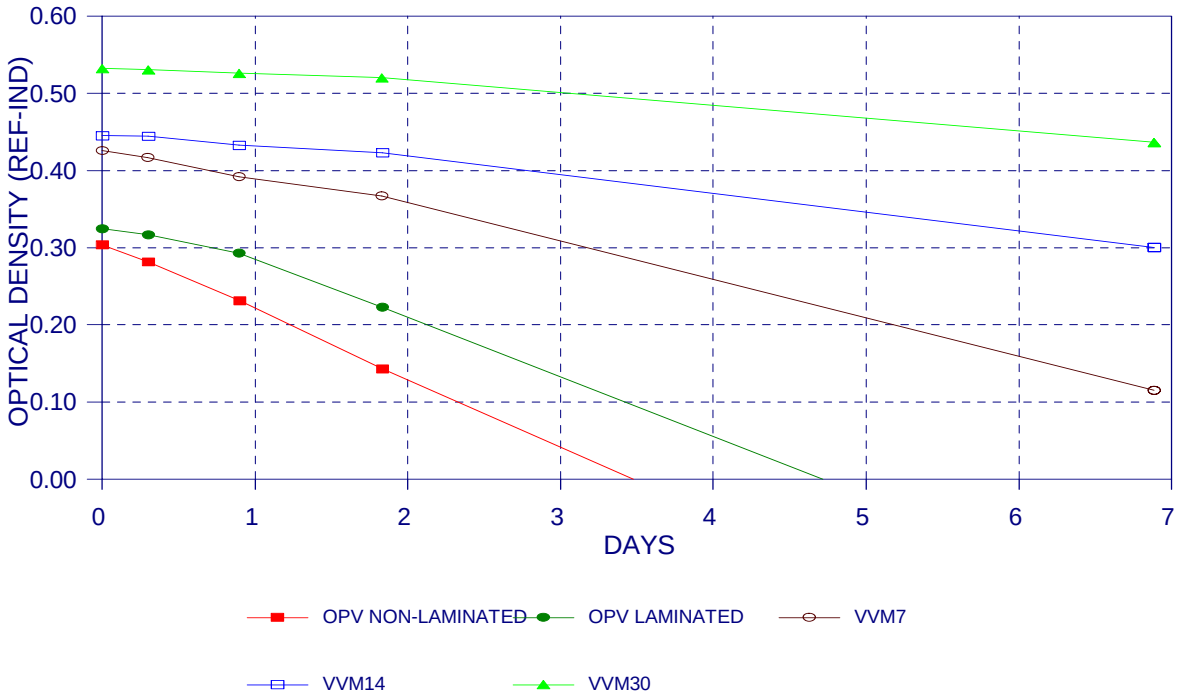


**Effect of direct sunlight through a window on VVM color development**



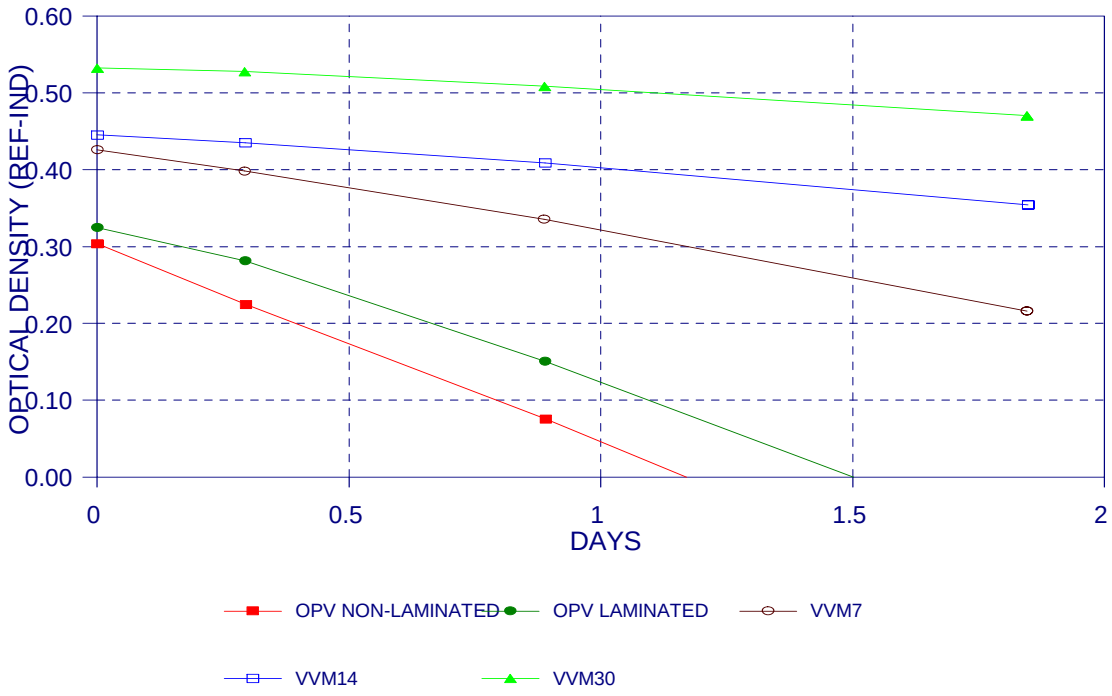

Direct sunlight through a tinted glass window has a significant impact on unlaminated VVM2, a less significant impact on laminated VVM2, and a smaller but measurable effect on VVM7, VVM14 and VVM30 after 2.5 hours. Unlaminated VVM2 reaches the endpoint in less than 3 hours.

**Figure 5.2.4**
**Effect of fluorescent lights in laboratory on color development of VVMs**




Typical fluorescent lighting found in control laboratories or other indoor areas has a very small impact on VVMs during routine handling times. Unlaminated VVM2 reaches the endpoint in about 3.5 days, while laminated VVM2 reaches the endpoint in about 4.6 days.

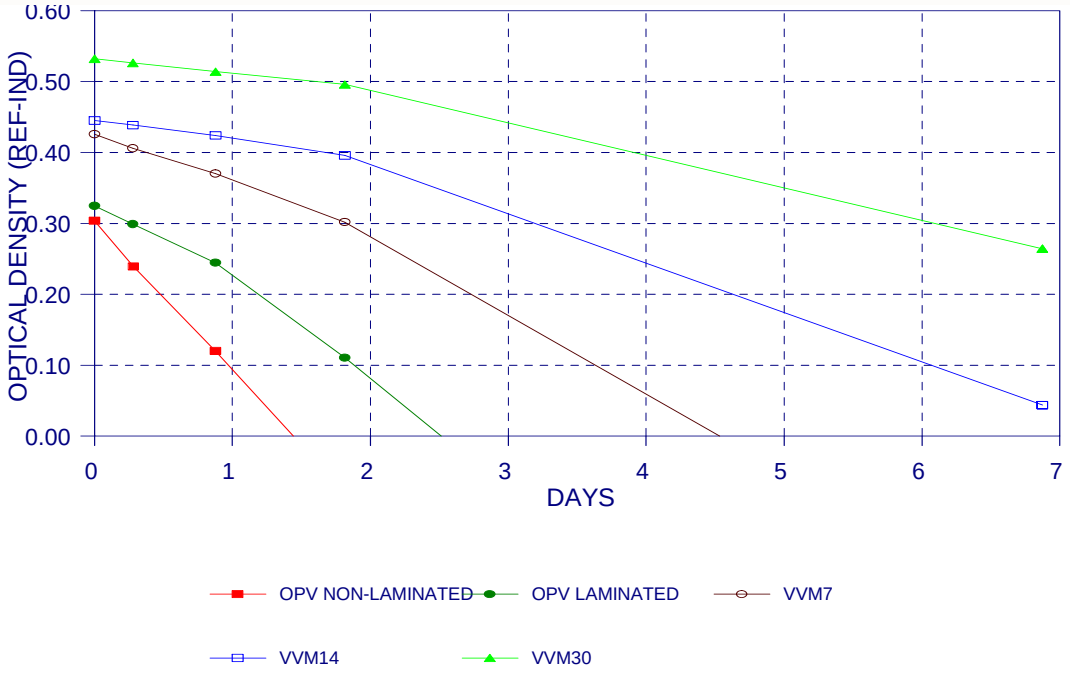
**Figure 5.2.5**
**Effect of incandescent light on VVM color development**




Incandescent light can cause color development of VVMs during time as shown in Figure 5.2.5. This result was interesting because it is commonly believed that incandescent bulbs do not emit UV light. Data from the radiometer measurements of the UVA + UVB content confirm that there is more UV from a 60W bulb at a distance of 10 inches than there is from a fluorescent lamp in the lab at 7 feet. The endpoint for unlaminated VVM2 is about 1.2 days and for laminated VVM2 is about 1.5 days.

**Figure 5.2.6**

**Effect of ambient light in manufacturing plant on VVM color development**




High intensity lighting in the manufacturing plant can cause a small impact on VVM2 (about 0.01 OD in 1 hour, on unlaminated VVM2 as shown in Figure 5.2.6). Exposure of VVMs to ambient lighting during manufacturing at TEMPTIME is minimal, normally less than a minute as the manufacturing process is high speed and the VVMs are rolled up and therefore not exposed to light. Unlaminated VVM2 reaches the endpoint in about 1.4 days, laminated VVM2 in about 2.5 days, while VVM7 is about 4.5 days.

### 5.3 Practical Summary of OD change with light under different conditions

The results of the effect of ambient light on the color of the active portion of the VVMs are summarized in the table below. Entries for this table were calculated by subtracting the change in optical density due to time-temperature exposure measured in the dark control, if any, from the optical density change of test articles stored in the light. The table is meant to provide a general guide for the impact of various lighting conditions of the VVMs.

| ***Practical summary of OD change due to different light exposures*** | | | | | | |
|---|---|---|---|---|---|---|
| VVM Type | Direct Sun | Shade | Direct Sun Through Window | Fluorescent Light – Lab | Fluorescent Light – Plant | Incandescent Light |
| **Exposure Time**** | **30 Minutes** | **30 Minutes** | **43 Minutes** | **7 hours** | **7 hours** | **7 hours** |
| VVM30 | 0.04 | 0.01 | 0.01 (estimated) | 0.00 | 0.01 | 0.00 |
| VVM14 | 0.05 | 0.00 | 0.01 | 0.00 | 0.01 | 0.01 |
| VVM7 | 0.12 | 0.02 | 0.02 | 0.00 | 0.01 | 0.02 |
| VVM2 | 0.30 | 0.05 | 0.04 | 0.01 | 0.03 | 0.04 |
| VVM2 unlam | 0.47 | 0.11 | 0.13 | 0.02 | 0.06 | 0.07 |

** 30 minutes, 43 minutes, and 7 hours chosen for analysis have no specific reason except for the practical aspects of measurement during the day. These test intervals are common to all VVM types in their specific test condition.

Data show that under all conditions studied, each type of VVM is sensitive to light. The sensitivity to light is greatest for VVM2 with no overlamination (the most used construction for VVM2) followed by VVM2 with lamination, then VVM7, then VVM14, then VVM30.

Section 7 of this report contains graphs of the optical density change as a function of exposure time in the various test conditions. Raw data of the optical density results are contained in Annex B.

## 6. Recommendations for VVM Handling During Storage and Use

Due to the sensitivity of VVMs to light, these recommendations are very important to preserve the initial start OD.

6.1. Storage of VVMs
- 6.1.1. Store VVMs in a dark freezer, or shield them from light.

6.2. Label Application
- 6.2.1. The time used for labeling VVMs to vaccine vials or other packaging should be as short as possible to avoid exposure to light.
- 6.2.2. Avoid any exposure of direct sunlight through a window during VVM handling and labeling operations.
- 6.2.3. Use cool white fluorescent light.

6.2.4. Use UV filters on lights where potential exposure times may be longer than several minutes.
6.2.5. Avoid UV lights used for killing insects.
6.2.6. Under normal conditions of less than one hour exposure under typical indoor lighting, there should be no measurable impact of light on VVMs.

6.3. Storage of Labeled Vials
6.3.1. Store vials labeled with VVMs in the dark, or shield them from light.

6.4. Control lab
6.4.1. Samples should be measured quickly after removal from test conditions and promptly placed back in the proper storage area after measurements are completed.

6.5. Field Use – vials should be protected from light during transport, storage, and final use in the field.

## 7. Graphs of results and pictures of test conditions

### 7.1. *Direct Sunlight*

Samples were placed outside on cement pavement in full sun exposure on a bright sunny day (August 7, 2002). This day was chosen because of the clear, mostly cloudless sky. The samples in the foil control bag were placed next to the exposed samples. Readings of the sun intensity were taken and recorded each time the samples were being brought into the laboratory for optical density measurements. The average temperature was 42.0EC and the average relative humidity was 28.4% as calculated from the HOBO logger data. UVA + UVB intensity measured with the radiometer ranged from 3,100 – 5,200 µmW/cm$^2$. Readings of light intensity from the HOBO dataloggers were off scale, > 600 lumen/ft$^2$. Photographic light meter gave values between 131,500 - 350,000 Lumen/M$^2$.

**Figure 7.1.1**
**VVM samples and control in direct sunlight.**


*Figure 7.1.1 shows the five VVMs of each type attached to the white card and placed on the concrete pavement in direct exposure to the sun. The foil pouch containing the control samples (no light) is shown on the left.*

## Figure 7.1.2
**Effect of direct sunlight on VVM color development**

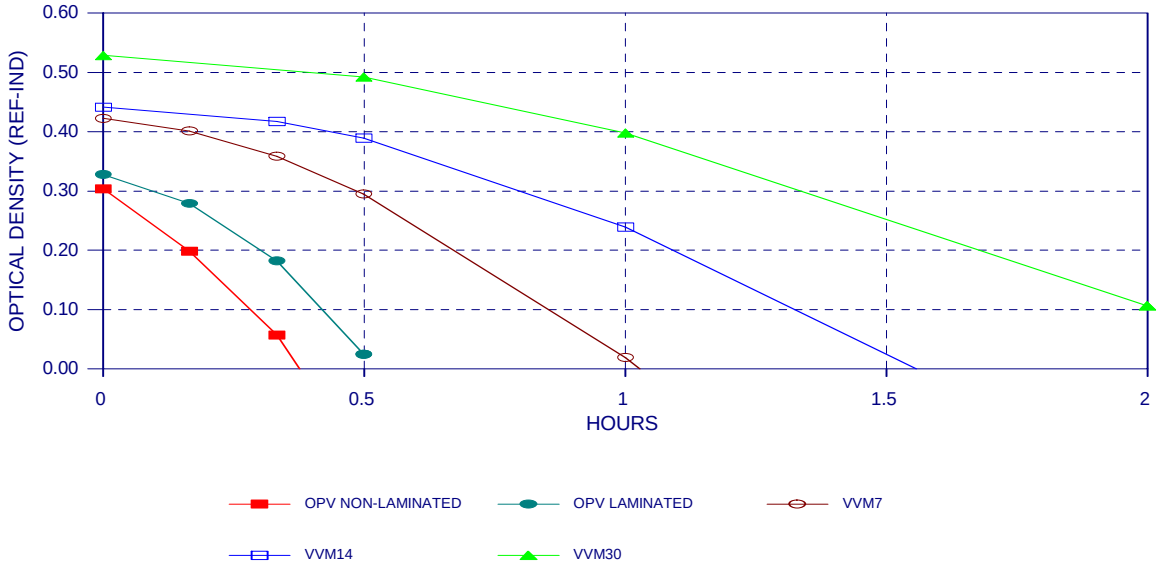
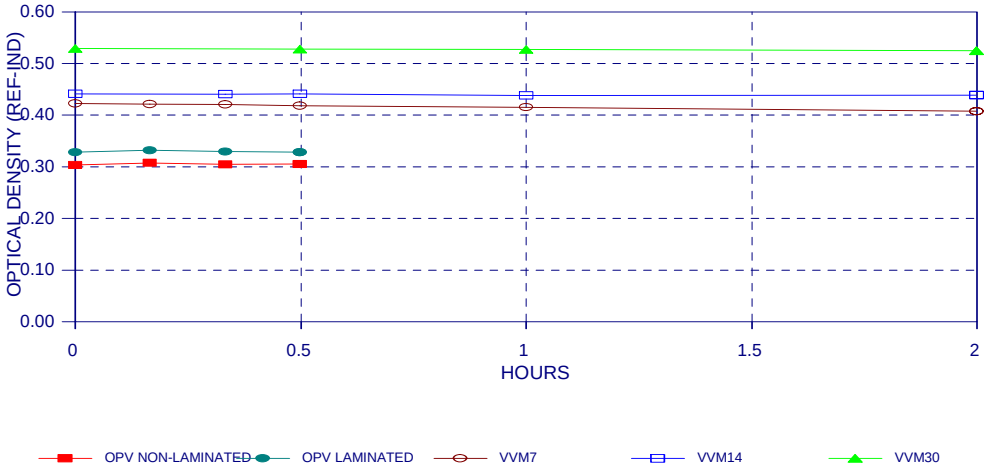



*Figure 7.1.2 shows that direct sunlight has a very inmportant impact on the optical density change of each type of VVM. The optical density in all figures is reported as the difference between the reference ring and the indicator. As the indicator gets darker, the difference in optical density shown in the graph gets smaller. The endpoint of the indicator is when the difference between the reference ring and indicator equals 0.00. The difference in start OD of each VVM type is typical: start OD approximately 0.30 for VVM2, 0.40 for VVM7 and VVM14, 0.50 for VVM30.*

## Figure 7.1.3
**Control (dark) samples for direct sunlight test**




*7.1.3 shows that there is no change in optical density of the VVMs kept in the dark during the test period.*

## Figure 7.1.4
**UVA + UVB Radiometer Measurements in direct sunlight**

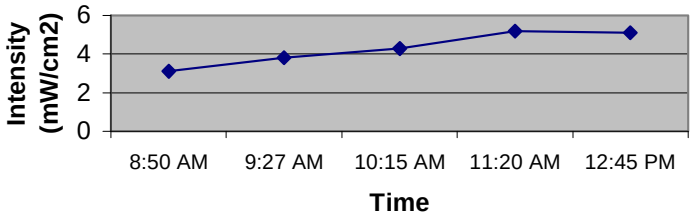
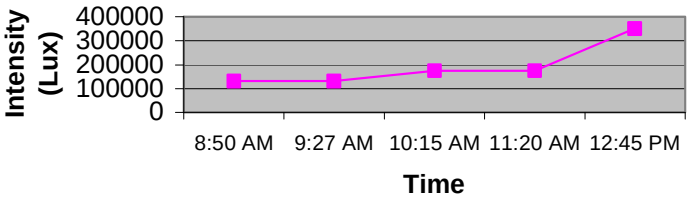
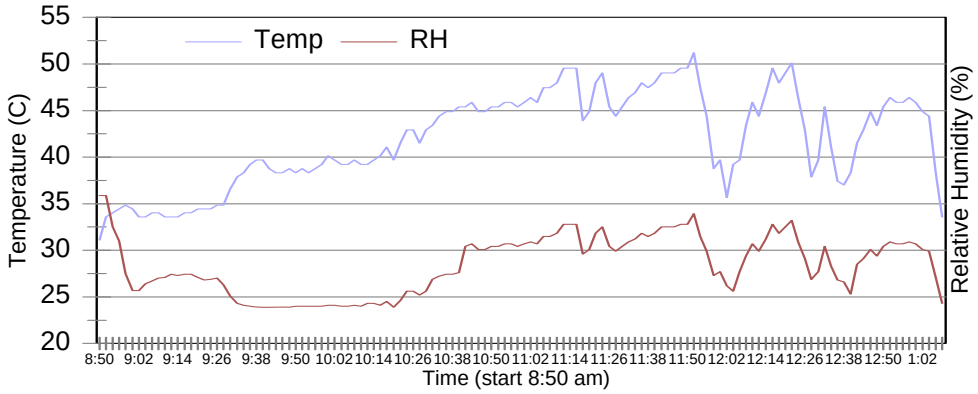



*Figure 7.1.4 shows the instantaneous intensity of the UVA + UVB light at the time when the samples were removed for measurement of optical density. Figure 7.1.5 shows light intensity measured with the photographic light meter.*

## Figure 7.1.5
**Photographic Light Meter Measurements in direct sunlight**




## Figure 7.1.6
**HOBO data logger readings of temperature and relative humidity in direct sunlight**
(Temperature in Blue; Relative Humidity in Red)



7.2 ***Indirect sunlight (shade)***

Samples were placed outside in shade at the same time as the samples were in direct sunlight. They were placed behind a building sign so no full sun exposure was available. The samples in the foil control bag were placed next to them. Radiometer readings of the UVA + UVB intensity and readings from the photographic light meter were taken and recorded each time the samples were removed for optical density measurements. UVA+UVB measurement and ranged from 200 to 500 µmW/cm$^2$. Photographic light meter readings ranged from 4,150 to 44,000 Lumen/M$^2$. The average temperature was 26.3EC and the average relative humidity was 35.4% as calculated from the HOBO logger data. Readings of light intensity from the HOBO data logger were off scale, > 600 Lumen/ft$^2$.

**Figure 7.2.1**
**Samples and control in shade of building sign**


*Figure 7.2.1 shows the samples and dark control in the shade behind a building sign. Samples were brought to the laboratory for measurements of optical density at the same times as the direct sunlight samples.*

## Figure 7.2.2
**Effect of indirect sunlight on VVM color development**

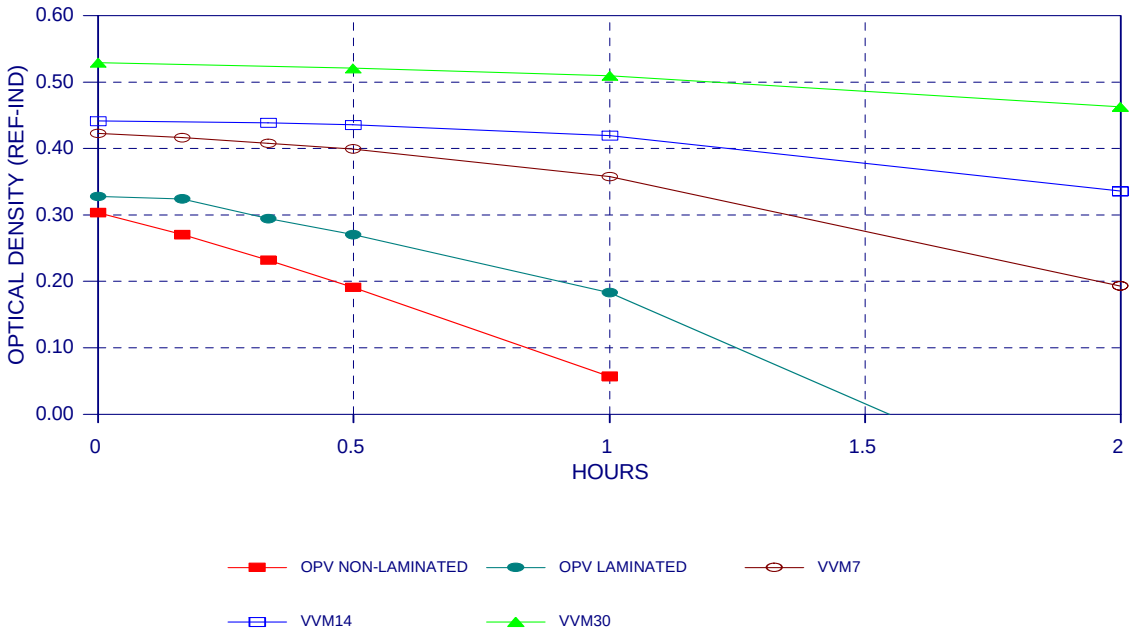



*Figure 7.2.2 shows that indirect sunlight (shade) has a very significant effect on the color development of all VVMs. The impact is less than that of direct sun exposure.*

## Figure 7.2.3
**Control (dark) samples for indirect sunlight (shade) test**

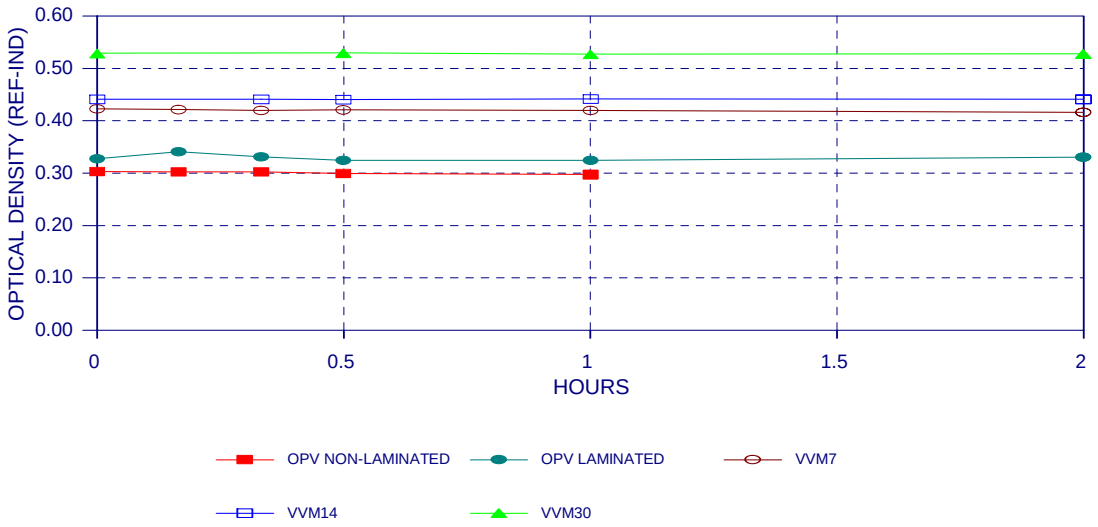



*Figure 7.2.3 shows there is no measurable optical density change of the dark control during the test period.*

## Figure 7.2.4
**UVA + UVB Radiometer Measurements in indirect sunlight (shade)**

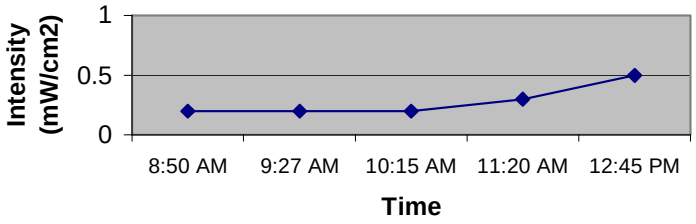
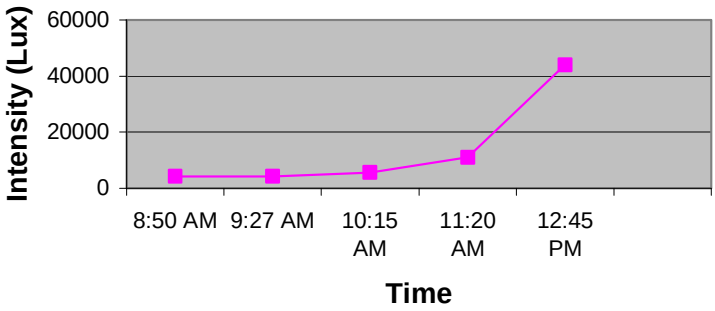
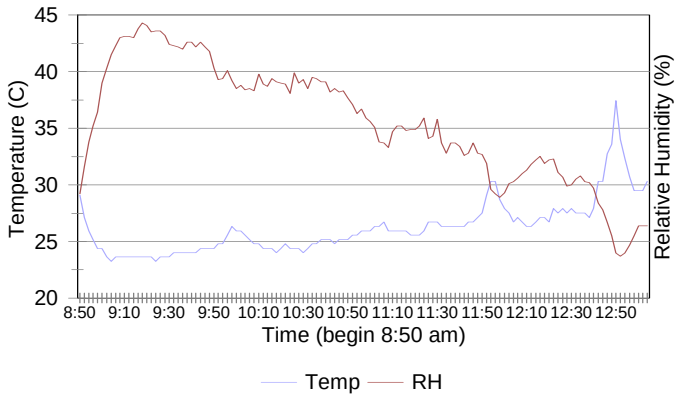



*Figure 7.2.4 shows the instantaneous intensity of the UVA + UVB light at the time when the samples were removed for measurement of optical density while Figure 7.2.5 shows the light intensity as measured with the photographic light meter.*

## Figure 7.2.5
**Photographic Light Meter Measurements in indirect light**

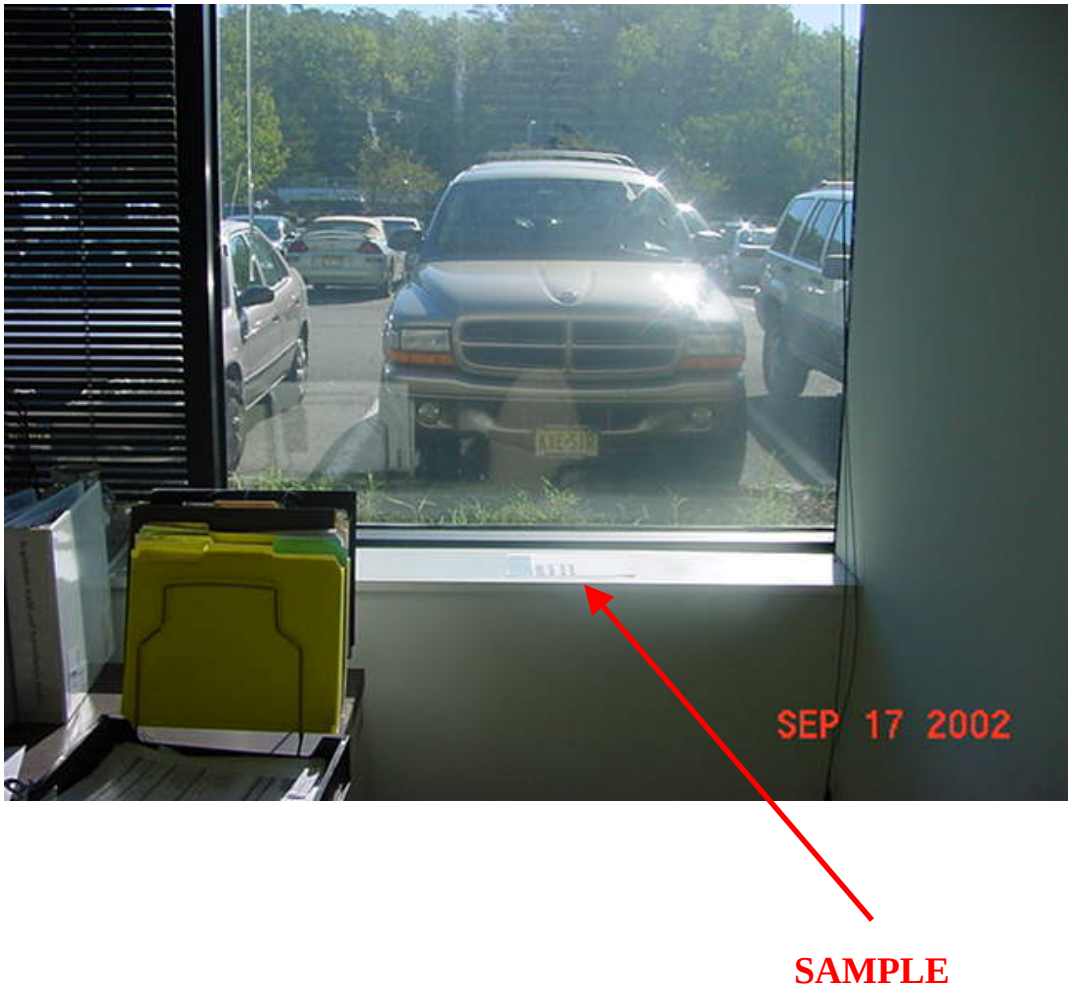



## Figure 7.2.6
**Temperature and humidity data from HOBO datalogger placed in shade**
(Temperature in Blue; Relative Humidity in Red)



7.3 ***Direct Sunlight through a window*** – Figure 7.3.1 shows samples placed on an office windowsill with direct exposure to the sun coming through the window. Readings of the sun intensity were taken and recorded at every optical density measurement. UVA+UVB measurement and ranged from 300 to 1,700 µmW/cm$^2$. Photographic light meter readings ranged from 5,500 to 22,000 Lumen/M$^2$. The average temperature was 29.0EC and the average relative humidity was 27.0% as calculated from the HOBO logger data. Readings of the light intensity from the HOBO datalogger were off scale, > 600 Lumen/ft$^2$.

**Figure 7.3.1**
**Samples and control in direct sunlight through a window**



## Figure 7.3.2
**Effect of direct sunlight through a window on VVM color development**

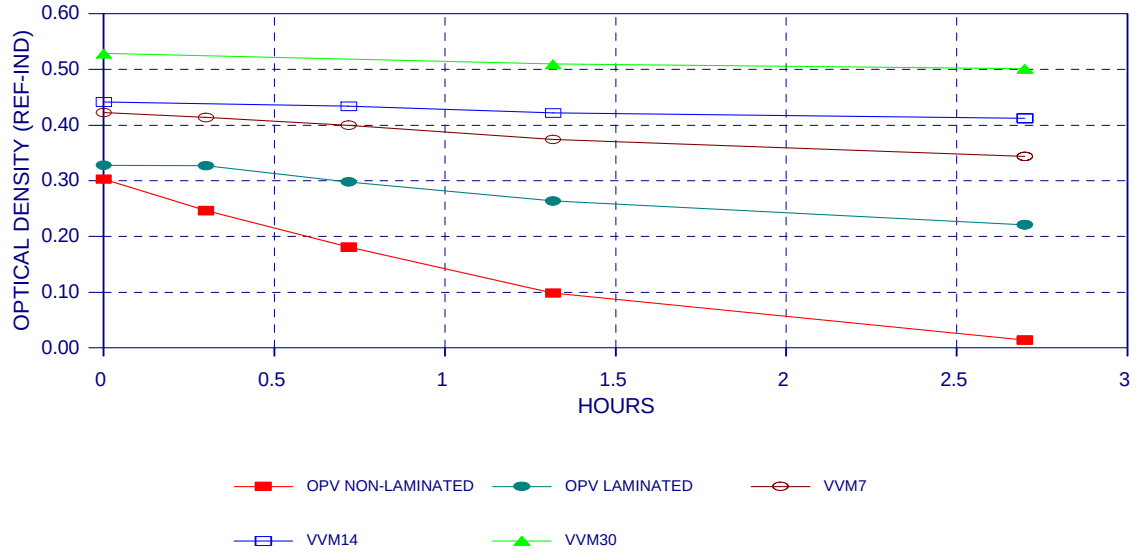



*Figure 7.3.2 shows that there is a significant impact of direct sunlight coming through a window on unlaminated VVM2 during several hours. The impact is less significant than direct sunlight due to the UV blocking effect of the window*

## Figure 7.3.3
**Control (dark) samples for direct sunlight through a window**

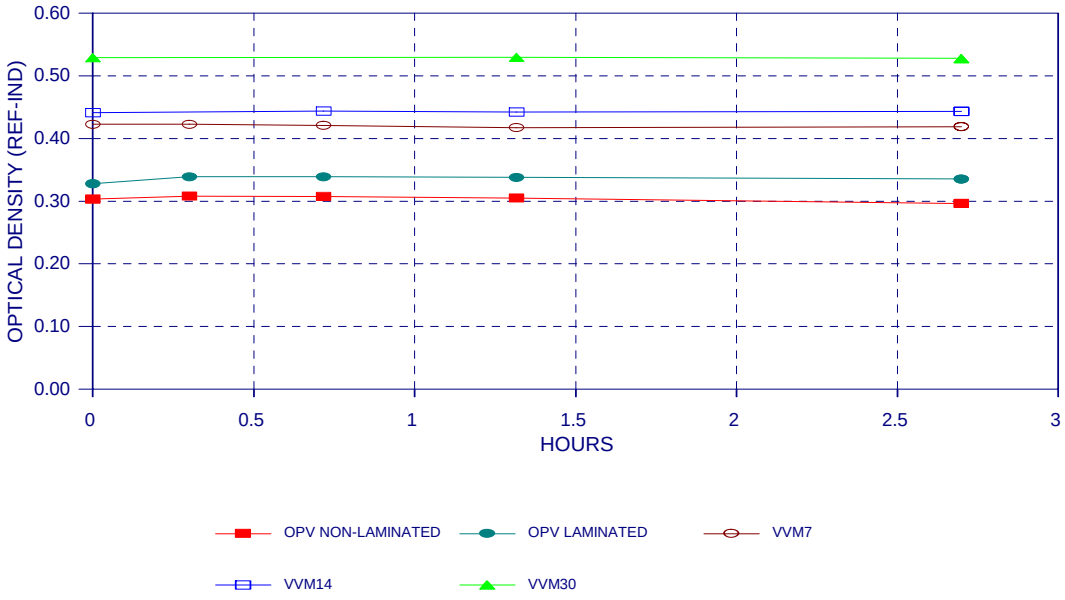



*Figure 7.3.3 shows that there is no color change of the VVMs while stored in the dark during this exposure period.*

**Figure 7.3.4 - UVA + UVB Radiometer Measurements in direct sunlight through a window**

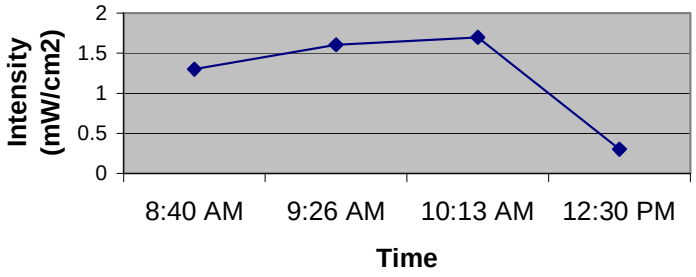



*Figure 7.3.4 shows the instantaneous intensity of the UVA + UVB light at the time when the samples were removed for measurement of optical density while Figure 7.3.5 shows the light intensity as measured with the photographic light meter.*

**Figure 7.3.5 - Photographic Light Meter Measurements - direct sunlight through a window**

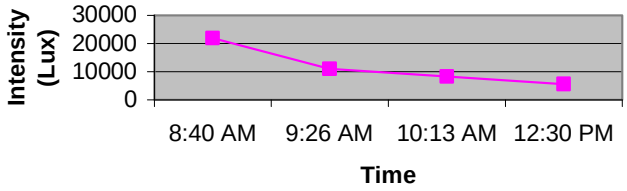
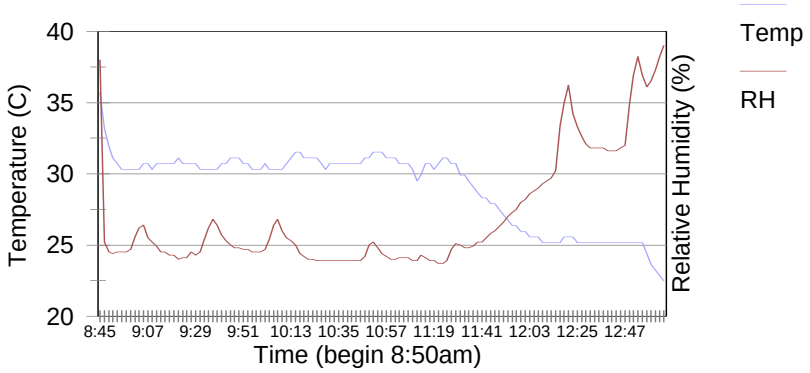



*Figure 7.3.4 and 7.3.5 show data from the radiometer and photographic light meter during the exposure of samples to direct sunlight through a window.*

## Figure 7.3.6

**Temperature and humidity data from HOBO datalogger while samples placed in direct sunlight on a windowsill** (Temperature in Blue; Relative Humidity in Red)



7.4 ***Artificial lighting - cool white fluorescent light*** - Samples were placed on a lab bench in a laboratory. Samples were 7 feet from the light source. The radiometer did not register any UV reading (power density < 1 µW/cm2), and a photographic light meter measured intensity as 350 Lumen/$M^2$. The average temperature was 23.3EC, and the average relative humidity was 54.9% as calculated from the data taken by the HOBO. The light intensity measured with the HOBO logger averaged 74 Lumen/$ft^2$

**Figure 7.4.1**
**Samples exposed in laboratory with cool white fluorescent lights**


*Figure 7.4.1 shows research laboratory #1 where the test was performed.*

Figure 7.4.2
Effect of fluorescent lights in laboratory on color development of VVMs

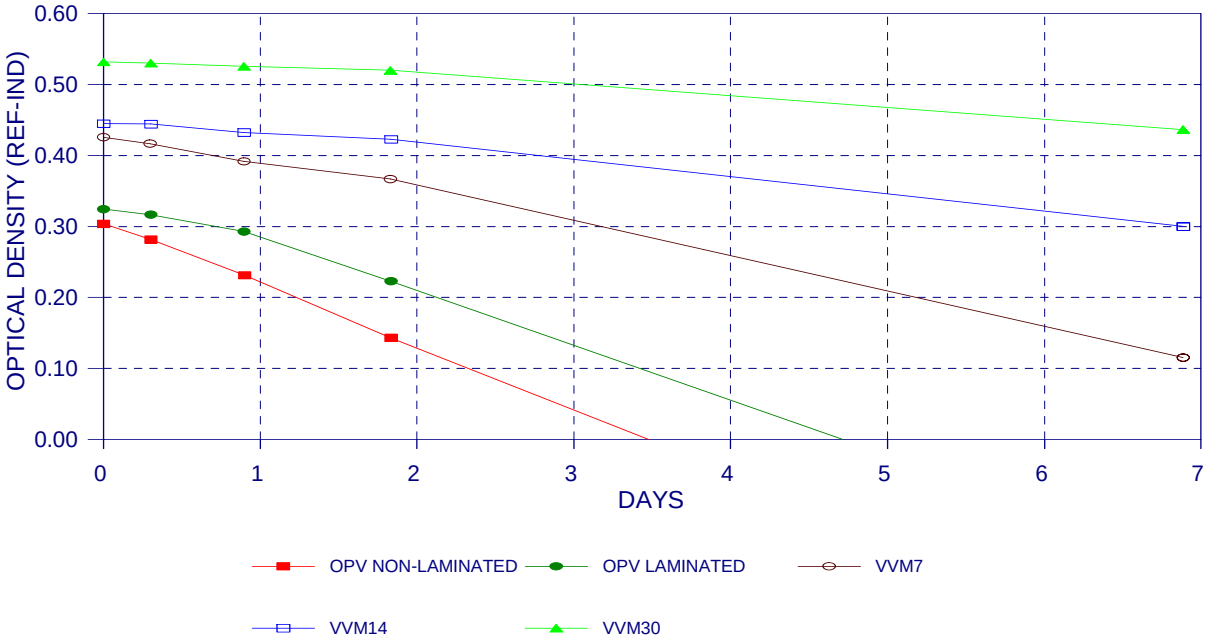



*Figure 7.4.2 shows that VVMs can be affected by light from typical fluorescent lighting over a long period of time (days). This reinforces the recommendation that samples be measured quickly after removal from test conditions and prior to being measured.*

Figure 7.4.3
Dark control during laboratory exposure

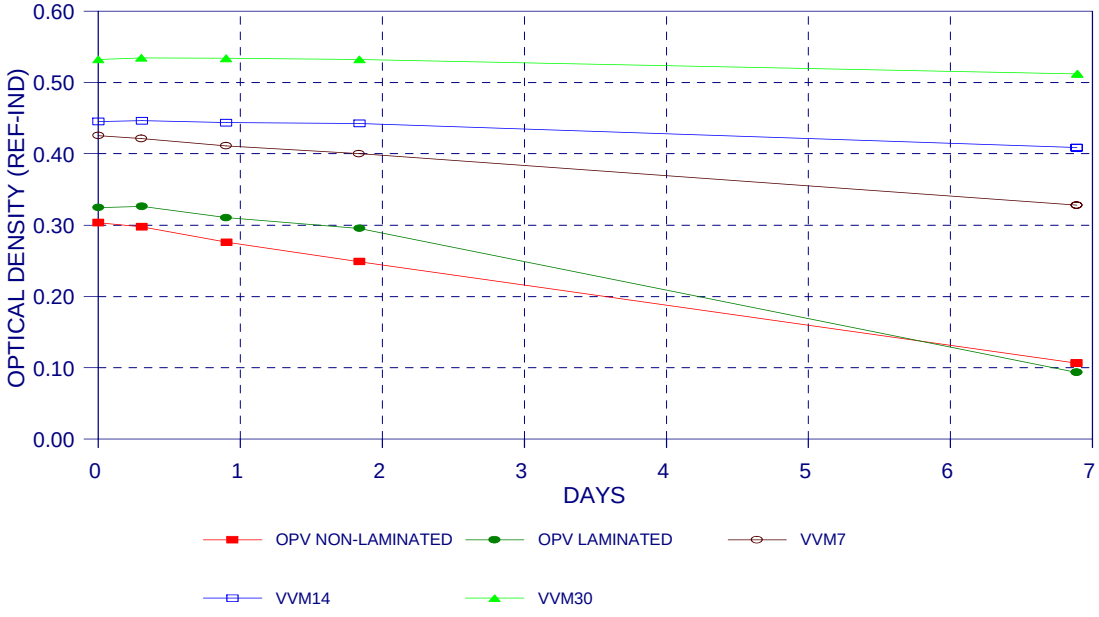


**Figure 7.4.4**

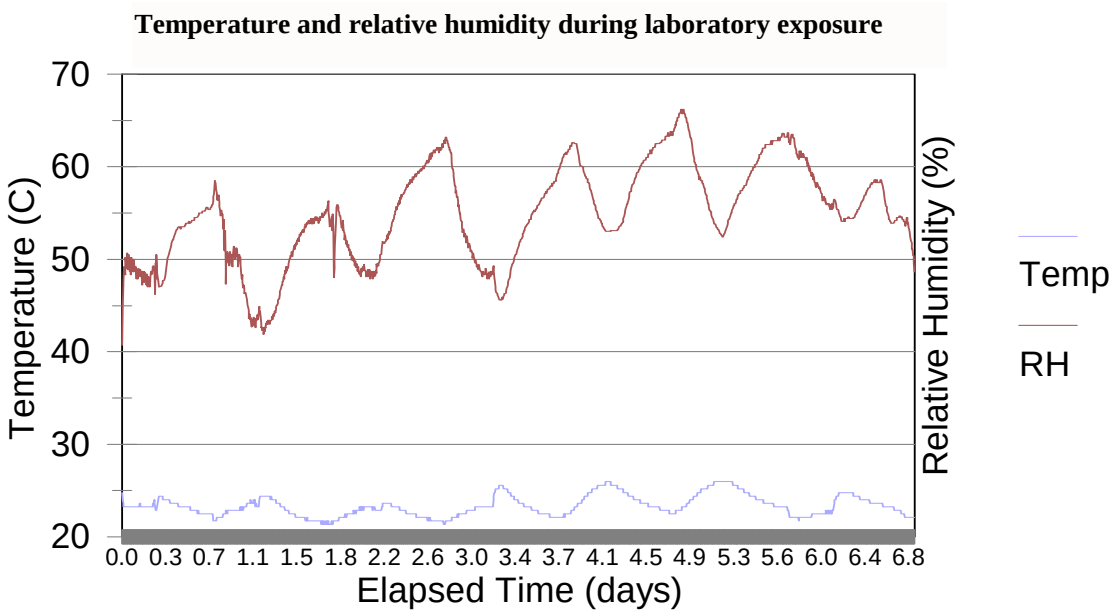



**Figure 7.4.5**
**Light Intensity measured with HOBO**

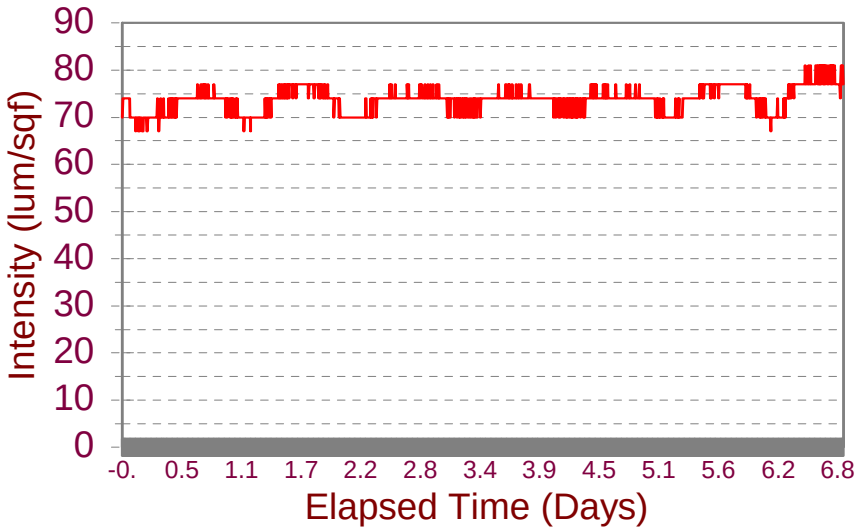



*Figure 7.4.4 shows the temperature and relative humidity in the laboratory during the study while Figure 7.4.5 shows the intensity of the common fluorescent lighting in the lab.*

7.5 ***Artificial lighting – incandescent light***

Samples were placed 10 inches from a 60 W incandescent light. Light intensity was 2 μW/cm2 and 700 Lumen/$M^2$. The incandescent light was the only light source in the darkened room.

**Figure 7.5.1**
**Samples stored in incandescent light**

*Figure 7.5.1 shows the position of the test samples in the 2nd floor telephone switching room.*

Figure 7.5.2
Effect of incandescent light on VVM color development

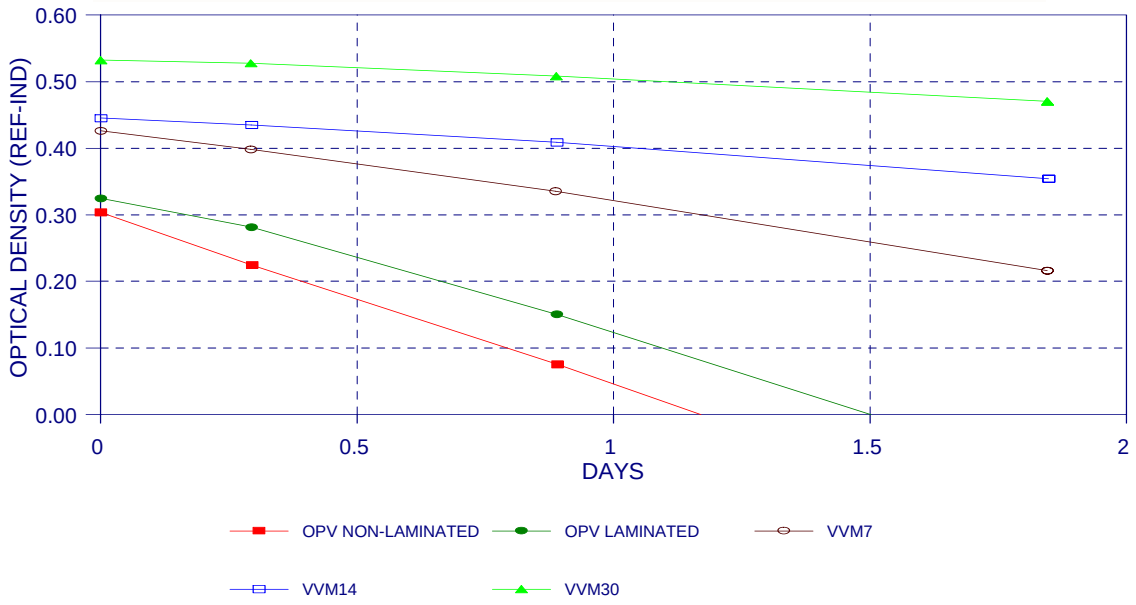



*Figure 7.5.2 shows that an incandescent lamp can cause color development of VVMs during time. This result was interesting because it is commonly believed that incandescent bulbs do not emit UV. Data from the radiometer measurements of the UVA + UVB content in fact confirms that there is more UV from a 60W bulb at a distance of 10 inches than there is from a fluorescent lamp at 7 feet.*

Figure 7.5.3
Dark control during incandescent light exposure

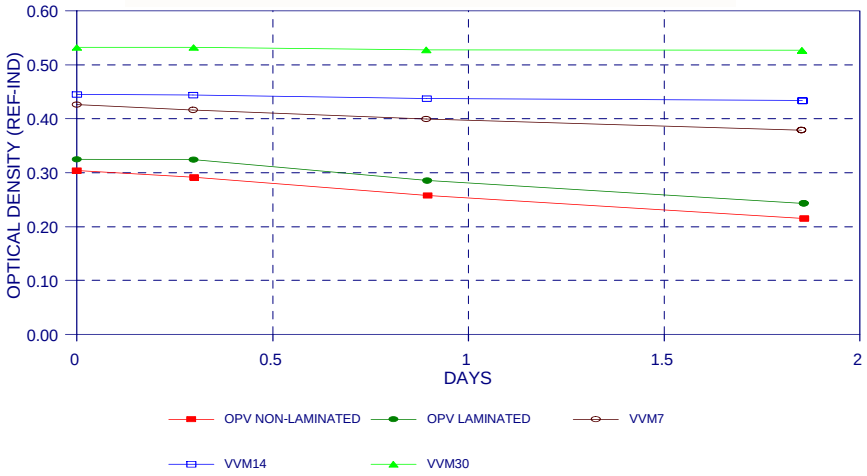



*Figure 7.5.3 shows the dark control color development. The color development in this chart is due to time and temperature effects since the temperature was rather warm in this room (31.7°C).*

**Figure 7.5.4**

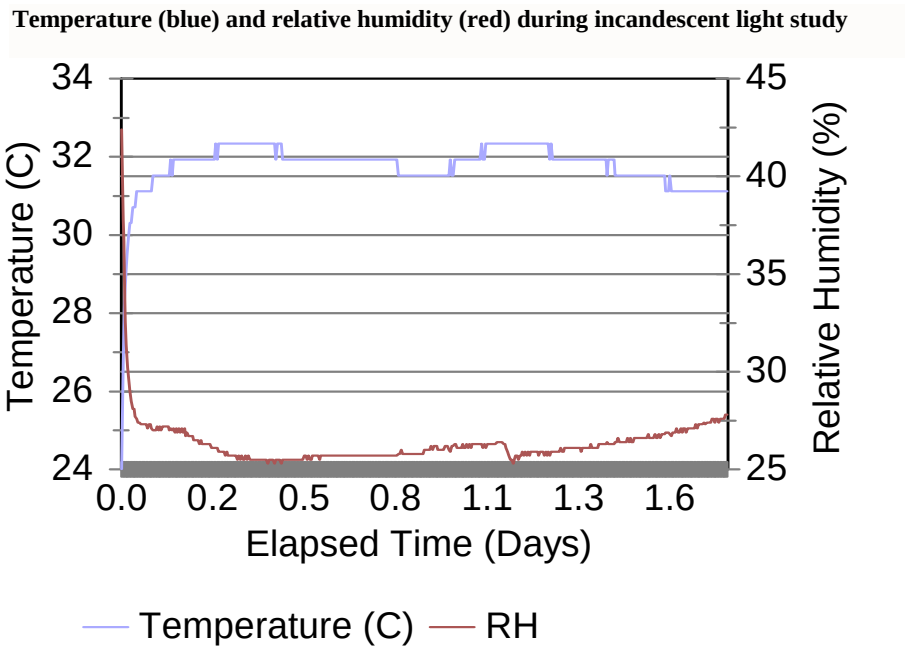



**Figure 7.5.5**

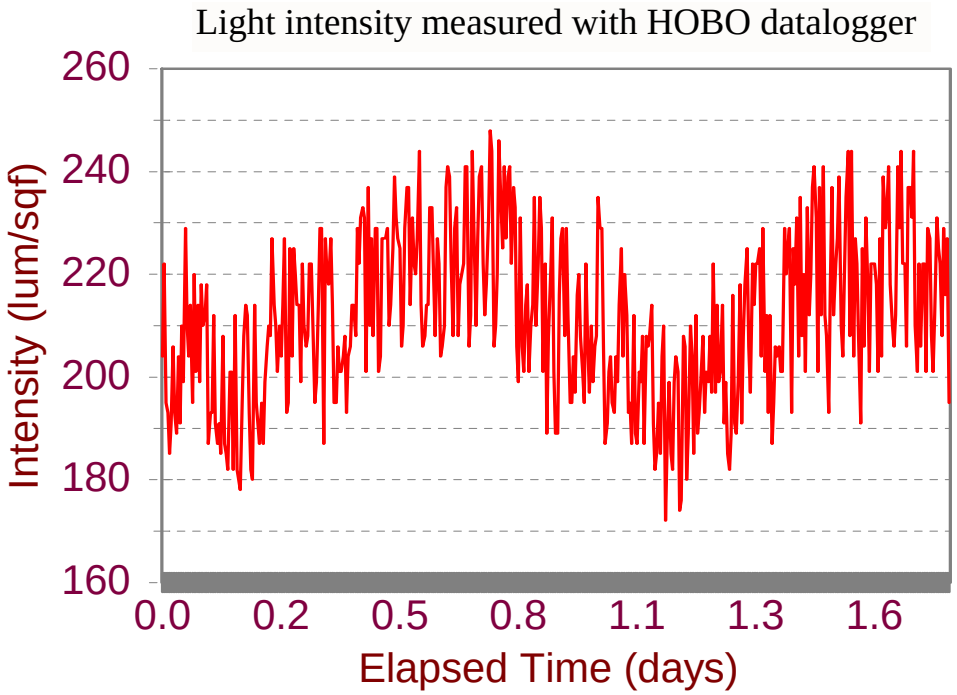



*Figure 7.5.4 shows the temperature and humidity during the incandescent light study. Figure 7.5.5 shows the light intensity from the incandescent bulb during the study as measured by the datalogger.*

Samples were placed on top of a shelf in the manufacturing plant. Samples were approximately 11 and 14 feet from high-output fluorescent bulbs (type F96T12HO) and approximately 22 feet from metal Halide bulbs (400 watt, 277 volts). A radiometer measured the intensity (power density) as 009 µW/cm2, and a photographic light meter measured intensity as 350 lux. The average temperature was 22.0EC, the average relative humidity was 62.3%, and the average intensity was 55.8 lumens/ft $^2$ as calculated from the data taken by the HOBO.

**Figure 7.6.1**
**Samples stored in a highly lit manufacturing area**

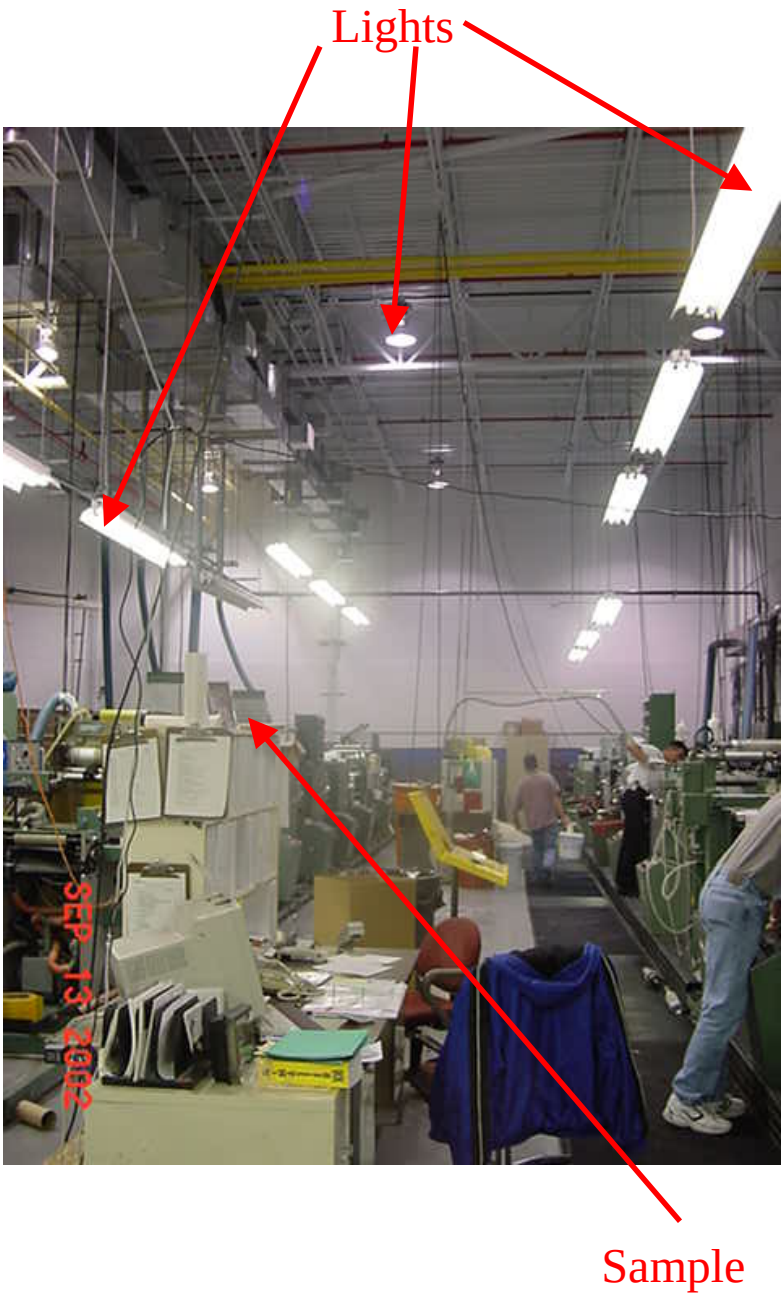
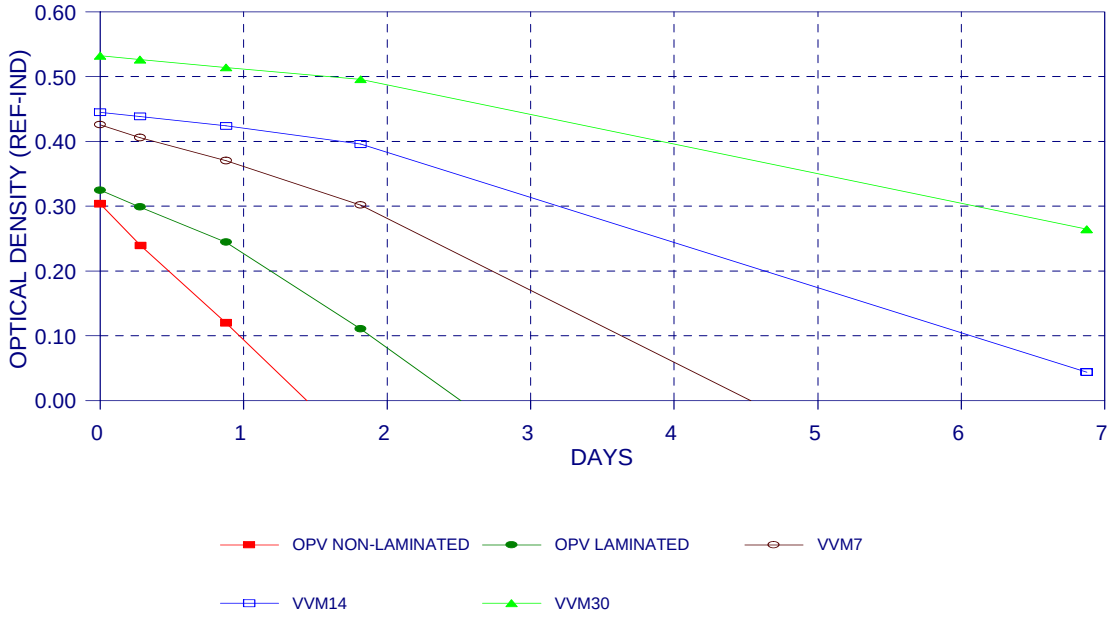



*Figure 7.6.1 shows the location of the samples in the printing area at TEMPTIME Corporation.*

Figure 7.6.2
Effect of ambient light in manufacturing plant on VVM color development




Plant lighting can have a small impact on VVM2 ( about 0.01 density change in 1 hour). This finding is consistent with the UV intensity measured with the radiometer being highest in the plant, followed by the incandescent light, then normal fluorescent lighting. The impact of the plant lighting on VVM7, 14 and 30 is much reduced (see Figure 7.6.2).

Figure 7.6.3
Dark control during plant study

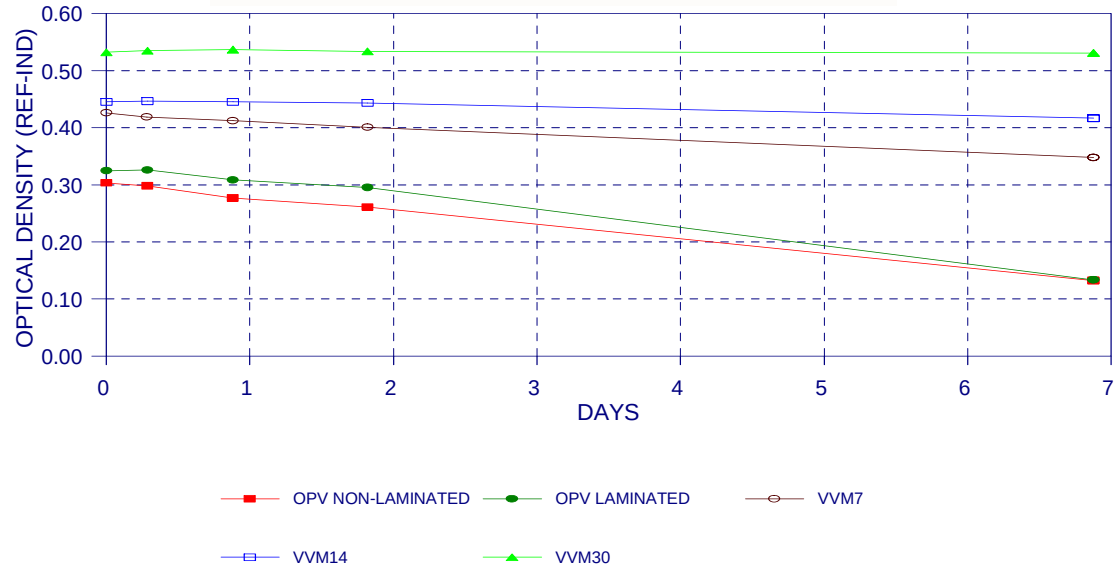



*Figure 7.6.3 shows the expected change in OD of the dark control due to time and temperature exposure.*

**Figure 7.6.4 - Manufacturing plant**
Temperature and humidity

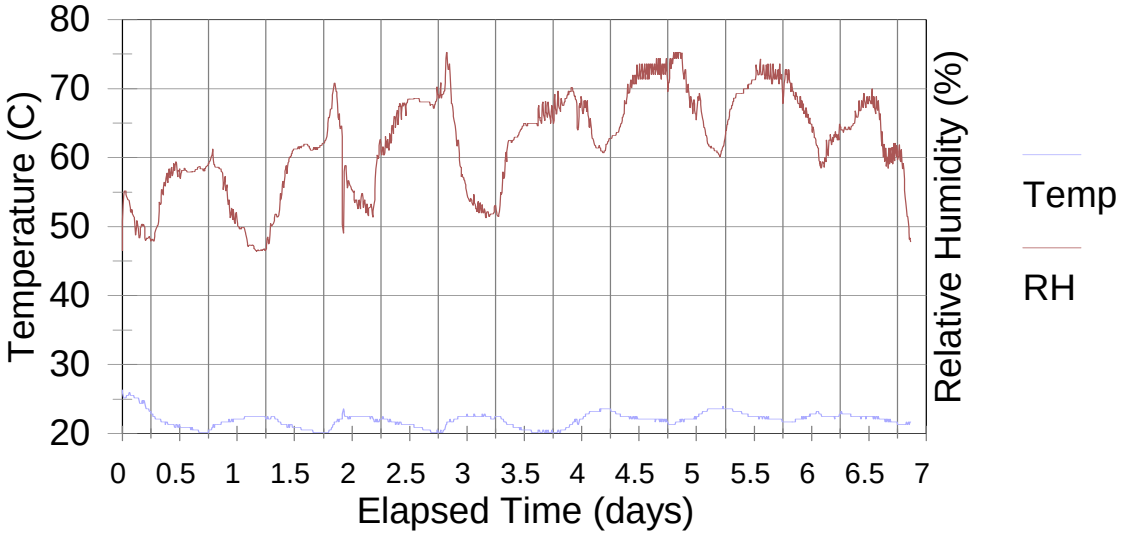



**Figure 7.6.5**

**Datalogger light intensity during plant study**

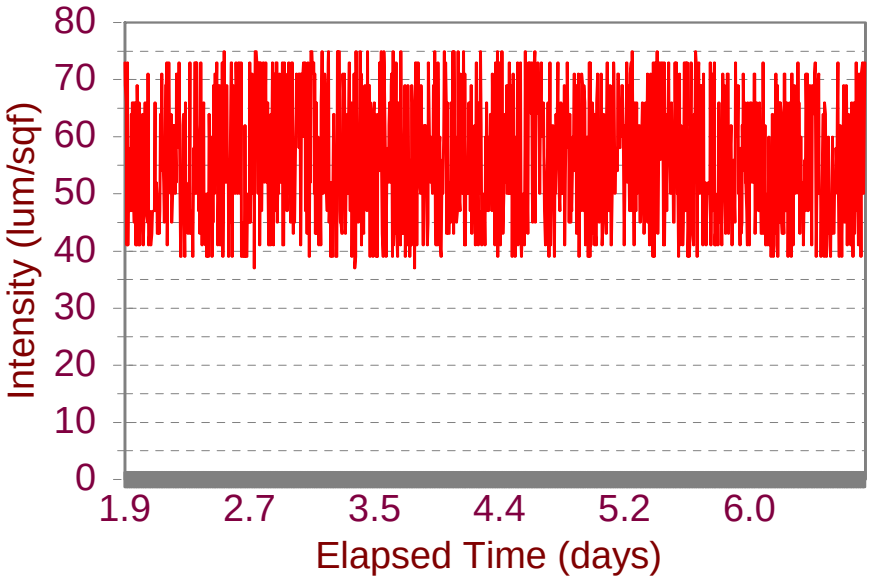



*Figure 7.6.4 shows the temperature and relative humidity of the plant during the study. Figure 7.6.5 shows the light intensity as measured with the datalogger. Note that the lights were left on during the entire study.*

# Annex A



# Certificates of Analysis

# Annex B
# Optical Density Data from Each Study

*This Annex is large (60 pages) and intentionally left blank to save space.*

*Data will be provided upon request.*

1

## Specifications for Vaccine Vial Monitors (VVM)

- PQS Performance Specification, Vaccine Vial Monitor (WHO/PQS/E06/IN05.1)
- General Specifications for HEATmarker® Time Temperature Indicators

2

## Testing Information

- Protocol for Testing and Releasing a Lot of HEATmarker® Vaccine Vial Monitors at 37°C
- Temperature Control Requirements for VVM End-point Determination

3

## Validation Information

- Practical Validation Procedures for Vaccine Vial Monitors
- PQS Independent Type-testing Protocol, Vaccine Vial Monitor (WHO/PQS/E06/IN05.VP.1)

4

## Practical Information

- Arrhenius graphs showing temperature-dependence for each category of VVM (-30 to +50°C and 0 to 40°C)
- Instructions for Use for Vaccine Vial Monitors
- Examples of full label and dot HEATmarker VVMs
- Effect of UV/Ambient Light Exposure on Color Development of HEATmarker® Vaccine Vial Monitors

5

## Commercial Information

- 2008 World-Wide Pricing Guide and General Conditions of Sale
- Special World-Wide Pricing Guide for UNICEF Tender Contracts (2007-2009) and General Conditions of Sale

TEMPTIME
The World Leader in
Time-Temperature Indicators

# 2008 World-Wide Pricing Guide
## *HEATmarker VVM (vaccine vial monitor)*
### *October 2007*
***Pricing is effective for all shipments made from 1 January 2008 - 31 December 2008***



NOTE: *ALL ORDERS ARE SUBJECT TO TEMPTIME' GENERAL CONDITIONS OF SALE WHICH AMONG OTHER THINGS, CONTAINS DISCLAIMERS OF WARRANTIES AND LIMITATIONS OF DAMAGES. NOTHING IN THIS PRICING GUIDE IS INTENDED TO ALTER TEMPTIME' GENERAL CONDITIONS OF SALE AS THEY MAY BE REVISED BY TEMPTIME FROM TIME TO TIME.*

## 1. Standard Specifications

**Definitions:**

**Full Label VVM (common label + time-temperature indicator)** – is a customized order specifically manufactured for one vaccine manufacturer, for one specific vaccine and for one specific type of VVM - 30 days @37ºC; 14 days@37ºC; 7 days @37ºC or 2 days@37ºC

**Dot VVM (time-temperature indicator only)** – is a standard TTI without text, one standard for each specific type of VVM: 30 days @37ºC; 14 days @37ºC; 7 days @37ºC and 2 days @37ºC.

| Specification | Full Label VVM | Dot VVM |
|---|---|---|
| *Minimum Order For One (1) Shipment* | 500,000 | 50,000 |
| *Standard Label Sizes* | 20mm X 44mm<br>57mm X 15mm<br>48mm X 18mm | 10mm dot (circle) |
| *Indicators Per Roll* | 10,000 | 10,000 |
| *Presentations* | 1 | 1 |
| *Rewind Direction* | 1 | 1 |
| *Core Size* | 76mm | 76mm |
| *Shipped by Container* | LD3 (in one shipment) | Insulated Cooler or an LD3 (in one shipment) depending on volume |
| *Number of Label Colors* | 1 | N/A |
| **Payment Terms & Conditions:** Pre-paid; 50% down-payment or Irrevocable Letter of Credit – Payable 30 days after shipment | | |
| **Deliveries:**<br>• *All deliveries are Ex Works TEMPTIME Corporation (Morris Plains, NJ – USA) See the General Conditions of Sale (Chapter 6). Shipment costs are not included in the prices in this price guide (dry ice, specific shipping container rental, inland transportation and air freight are all additional costs).*<br>• *All deliveries for the full label VVM described on page #3 and VVM dots for orders of 500,000 or greater, includes the fixed specific shipment preparation charge for one shipment* | | |
| **Handling Charge:** *The full label prices are established on quantities corresponding to one shipment, which includes the fixed specific shipment preparation charge. If a customer makes a specific request to receive an order in several shipments, the fixed specific shipment preparation charge ($500) will be added to each additional shipment, except if exactly equivalent to the rule in Chapter 3.* | | |

**1.3 Timing:** The pricing is valid for shipments for the period of January 1, 2008 through December 31, 2008 except for Indian manufacturers for which it is valid from April 1, 2008 through March 31, 2009.

**1.4 Special Orders** Any order different from these standard specifications will be quoted on a case-by-case basis (See Chapter 5).

## 2. Full Label VVM Prices in US Cents*

| Quantity by Shipment | VVM2<br>2 days @37ºC | VVM7<br>7 days @37ºC | VVM14<br>14 days @37ºC | VVM30<br>30 days @37ºC |
|---|---|---|---|---|
| 4,000,000+ | 4.05 cents | 5.11 cents | 5.21 cents | 5.34 cents |
| 2,000,000 | 4.29 cents | 5.28 cents | 5.41 cents | 5.49 cents |
| 1,000,000 | 4.57 cents | 5.58 cents | 5.66 cents | 5.89 cents |
| 500,000 | 5.13 cents | 6.22 cents | 6.30 cents | 6.42 cents |

Basic Price includes specific packaging & handling costs

***The price, in US cents, corresponds to the Standard Specifications defined on page 2 – Any order or request different from the Standard Specifications will be considered as a special request and quoted on a case-by-case basis (Ex: Sequential numbering).***

## Full Label VVM2 - Pricing Example:

| Quantity by Shipment | VVM Type | # Per Roll | Basic Price | *Total Costs By Shipment |
|---|---|---|---|---|
| 4 million | VVM2<br>2 days @37ºC | 10,000 per roll | 4.05 | $162,000 |
| 2 million | VVM2<br>2 days @37ºC | 10,000 per roll | 4.29 | $85,800 |
| 1 million | VVM2<br>2 days @37ºC | 10,000 per roll | 4.57 | $45,700 |
| 500,000 | VVM2<br>2 days @ 37ºC | 10,000 per roll | 5.13 | $25,650 |

***These costs include the specific handling costs but not the specific shipment costs.***

## 3. Dot VVM Prices in US Cents

| Quantity by Shipment | VVM2<br>2 days @37ºC | VVM7<br>7 days @37ºC | VVM14<br>14 days @37ºC | VVM30<br>30 days @37ºC |
|---|---|---|---|---|
| 4,000,000+ | 3.39 cents | 4.43 cents | 4.53 cents | 4.58 cents |
| 2,000,000 | 3.58 cents | 4.62 cents | 4.72 cents | 4.77 cents |
| 1,000,000 | 3.73 cents | 4.76 cents | 4.87 cents | 4.94 cents |
| 500,000 | 3.91 cents | 4.95 cents | 5.05 cents | 5.13 cents |
| Between 50,000 and 500,000 | * 3.94 cents | * 4.99 cents | * 5.09 cents | * 5.18 cents |

Basic Price includes specific packaging & handling costs

**** Rule for Packaging and Handling:*** ***TEMPTIME Corporation will add a fixed specific shipment preparation charge of $500 for each order below 500,000 units that are not shipped with another larger order. If orders below 500,000 are shipped with another order above 500,000 the specific shipment preparation charge will be waived***

***If two (2) orders (below 500,000 in total) are shipped together, TEMPTIME will add only one (1) $500 fixed charge for specific shipment preparation.***

***The shipment costs of dry ice, shipping container, inland freight and/or - airfreight are not included in the prices above.***

## Dot VVM30 - Pricing Example:

| Quantity by Shipment | VVM Type | # Per Roll | Basic Price | *Total Costs By Shipment |
|---|---|---|---|---|
| 4 million | VVM30<br>30 days @37ºC | 10,000 per roll | 4.58 cents | $183,200 |
| 2 million | VVM30<br>30 days @37ºC | 10,000 per roll | 4.77 cents | $95,400 |
| 1 million | VVM30<br>30 days @37ºC | 10,000 per roll | 4.94 cents | $49,400 |
| 500,000 | VVM30<br>30 days @37ºC | 10,000 per roll | 5.13 cents | $25,650 |
| 100,000 shipped alone | VVM30<br>30 days @37ºC | 10,000 per roll | 5.18 cents + $500 shipping & handling charge | $5,180+ $500 = $5,680 |
| 100,000 shipped with another order of 500,000 or larger | VVM30<br>30 days @37ºC | 10,000 per roll | 5.18 cents | $5,180 |

****These costs include the specific handling costs but not the specific shipment costs.***

## 4. Conditions of Delivery

4.1 Type of VVM
TEMPTIME will provide the VVM (VVM30: VVM14: VVM7: VVM2) only after the WHO has approved the use of the VVM for the vaccine. WHO approval is required for the first order of VVMs for each new vaccine.

4.2 Conditions of Delivery for VVMs
**TEMPTIME will provide a final delivery date upon receipt of the final customer approved artwork, VVM category approval by WHO, and receipt of the down-payment or Letter of Credit. If even one of the 3 items is missing, the order cannot be confirmed**.

4.3 Shipment Lead Time After Confirmation of the Order: Lead times are very different for the dot VVM, which are generally stored in TEMPTIME inventory and can be shipped in one week, and the full label VVM that requires a customized manufacturing for each order.

| | VVM Type | Dots | Full Label |
|---|---|---|---|
| ***Normal Lead Times*** | VVM2 | **1-3 weeks** | **3 to 5 weeks** |
| | VVM7 | **1-3 weeks** | **3 to 6 weeks** |
| | VVM14 | **1-3 weeks** | **4 to 7 weeks** |
| | VVM30 | **1-3 weeks** | **4 to 7 weeks** |

4.4 Certificate of Analysis: TEMPTIME Corporation supplies a Certificate of Analysis for each lot showing conformance with the WHO Specification for Vaccine Vial Monitors (VVM) E6/IN5, 25 March 2002 using TEMPTIME Testing Protocol **#QCLP P023-C – HEATmarker™ Vaccine Vial Monitor Release Testing Protocol** dated 03 April 2007 or **#P025 Protocol for Testing and Releasing a Lot of HEATmarker™ Vaccine Vial Monitors at 45ºC** dated 5 July 2004 and agreed by WHO that TEMPTIME can use under their responsibility.

4.5 Packaging: Each Shipment has a specific and proper packaging of the consignment with dry ice in accordance with the TEMPTIME Corporation General Conditions of Sale.

## 5. Special Requests (Additional Costs)
## (To be determined on a case-by-case basis)

5.1 Special Requests

Each "special request" will have an additional cost assigned to it by TEMPTIME. Examples of "special requests" that TEMPTIME may consider are:

(1) Full Label Orders Below 500,000 Units

(2) Size differential from the three (3) standard full label sizes

(3) Indicators per roll are less than 10,000

(4) Two (2) or more full label presentations for the same order

(5) Additional Rewinding

(6) Core Size different from 76mm standard

(7) Two (2) colors or more on a full label

(8) **Sequential Numbering**

a. **Available only with a full label**

b. **Minimum added cost of 0.25 cents per indicator**

c. **Additional lead time required of 2-4 weeks depending on quantity**

(9) Requests for Additional Liner at Beginning or End of the Roll

(10) Size of Label Greater than 880mm²

(11) Urgent / Rush Order

5.2 Quotes:

TEMPTIME will respond to any special request within a two (2) week timeframe by issuing a specific quotation.

TEMPTIME

The World Leader in Time-Temperature Indicators

## 6. GENERAL CONDITIONS OF SALE

## (TIME-TEMPERATURE INDICATORS)

**The Purchase and Sale.** Subject to the following terms and conditions, TEMPTIME Corporation ("TEMPTIME") agrees to sell to Buyer the products set forth on the attached order/confirmation or on an order/confirmation which refers to these General Conditions of Sale. Such products include threshold indicator products ("THI's") and time-temperature indicator products ("TTI's") (each of such products being referred to as "Indicators" in these General Conditions of Sale).

**Acceptance or Non-acceptance.** Each purchase of Indicators or any part thereof, by Buyer shall be made by an order from Buyer to TEMPTIME setting forth the purchase price and the date for shipment of the Indicators. No order, whether written or oral, shall be accepted unless confirmed in writing by TEMPTIME. TEMPTIME may accept or reject such order, at its sole discretion. If an order is accepted and confirmed, then the terms and conditions hereinafter set forth shall be applicable to each such order.

**Payment Terms.** Unless TEMPTIME has otherwise provided in a writing specifically relating to a Buyer's order, TEMPTIME requires, for all transactions, either a Letter of Credit acceptable to TEMPTIME for the benefit of TEMPTIME or a 50% down payment and acceptance of all orders shall be subject to receipt by TEMPTIME of either such down payment or the opening of such a Letter of Credit. Final and full payment is due and payable thirty (30) days after the date of TEMPTIME's final invoice and, if the Buyer has provided a Letter of Credit, TEMPTIME will draw upon the Letter of Credit at such time for the amount then due and payable unless the Buyer has otherwise paid such amount to TEMPTIME. All payments shall be made in U.S. dollars.

**Invoices.** TEMPTIME will issue a final invoice to the Buyer on the day the Indicators are shipped.

**Interest on Past Due Accounts.** Interest at the maximum legal rate or 1 1/2% per month, whichever is lower, may be charged by TEMPTIME on past due accounts. Such interest is due and payable by Buyer on receipt of an invoice therefor.

**Tolerance on Quantity.** When the Indicators are custom products (that is, products (i) other than those that contain only an Indicator (without text); (ii) which require non-standard chemistry and/or manufacturing processes and/or (iii) assembled to a card or label whose unique and specific characteristics prohibit the sale of the final product to customer other than the Buyer), TEMPTIME and the Buyer agree that TEMPTIME may manufacture for the Buyer Indicators pursuant to Buyer's order in quantities of between 100% - 110% of the amount ordered. The final invoice will reflect the actual quantity of custom products manufactured within the agreed tolerance. When the Indicators are other than custom products, TEMPTIME will produce Indicators in accordance with Buyer's order.

**Delivery and Risk of Loss.** All deliveries of Indicators are EXW TEMPTIME's manufacturing facility – Morris Plains (USA) (applying International Chamber of Commerce INCOTERMS 2000). The mode of shipment, including the carrier, shall be determined by Buyer. Buyer may ask TEMPTIME to arrange for shipping or recommend or choose a carrier or, should Buyer fail to instruct TEMPTIME, TEMPTIME will choose the carrier. Whether or not TEMPTIME so arranges shipping, Buyer shall bear the risk of loss upon TEMPTIME's placing the Indicators at the disposal of the Buyer or the carrier at TEMPTIME's manufacturing facility and, thereafter, TEMPTIME shall have no liability for loss or damage, whether incidental, consequential, direct, indirect, special or punitive, whether occurring from delays or damage, or otherwise. In all circumstances, Buyer shall pay the expense of shipment from TEMPTIME's manufacturing facility and if TEMPTIME shall incur such costs, Buyer shall reimburse TEMPTIME therefor upon the issuance by TEMPTIME to Buyer of an invoice with respect thereto.

**Inspection.** Promptly after the Indicators are delivered, and on the day of such delivery, Buyer shall inspect such Indicators for spoilage and damage. The failure of Buyer to inspect such Indicators promptly and on the day of delivery, and/or failure of Buyer to notify TEMPTIME of spoilage and/or damage of such Indicators within forty-eight (48) hours after delivery, shall operate as a full and complete waiver of all claims by Buyer that such Indicators are spoiled and/or damaged.

**Use and Storage of Indicators.** ***Indicators are not intended for use in direct contact with material intended for human consumption or for use on or in the human body. Accordingly, Buyer agrees not to use Indicators in such non-intended manner and shall indemnify and hold TEMPTIME and its affiliates harmless from any damages, claims or losses (including reasonable attorneys' fees and expenses) arising out of Buyer's breach of its obligation under this paragraph, including, without limitation, any violation of laws, rules or regulations applicable to materials and products for human consumption.***

Buyer shall not use Indicators that have spoiled or are damaged. If Buyer nevertheless uses such Indicators, TEMPTIME shall have no liability for any damages suffered in connection therewith and Buyer hereby indemnifies TEMPTIME and its affiliates against the same. Unless otherwise specified on the box in which the Indicators are packaged for delivery, all Indicators shall be stored by the Buyer at or below –24°C and in the absence of all light, and/or under such other conditions as TEMPTIME shall direct. Buyer shall "use" (meaning, apply the Indicators to Buyer's product) all Indicators delivered to Buyer on or before the "use by" date shown on the box in which such Indicators are packaged for delivery. If any of the Indicators fails to be so stored or used, TEMPTIME shall have no liability to Buyer for damages suffered in connection therewith, and Buyer hereby indemnifies TEMPTIME against the same, and TEMPTIME not have any obligation for replacement of such Indicators.

**DISCLAIMER OF WARRANTIES AND LIMITATION OF DAMAGES AS TO INDICATORS.**

**EXCEPT AS EXPRESSLY SET FORTH ON THE NEXT PAGE UNDER THE HEADING "STATEMENT OF LIMITED WARRANTY," TEMPTIME SPECIFICALLY EXCLUDES ALL WARRANTIES, EXPRESS OR IMPLIED, INCLUDING BUT NOT LIMITED TO WARRANTIES THAT THE INDICATORS ARE MERCHANTABLE AND THAT THE INDICATORS ARE FIT FOR ANY PARTICULAR PURPOSE. TEMPTIME SHALL HAVE NO LIABILITY FOR MONETARY DAMAGES RESULTING FROM DEFECTS IN THE INDICATORS, WHETHER OR NOT COVERED BY WARRANTY, INCLUDING BUT NOT LIMITED TO DAMAGES FOR LOSS OF PROFITS OR INCIDENTAL, CONSEQUENTIAL, DIRECT, INDIRECT, SPECIAL OR PUNITIVE DAMAGES.**

**Statement of Limited Warranty.** All Indicators are warranted to Buyer to perform substantially in conformance with the specifications provided with the "Quotation" or "Order Acknowledgement" sent from TEMPTIME to Buyer with reference to such Indicators (the "Order Specifications") or, if no such specifications are so provided, in accordance with TEMPTIME's internal specifications applicable to such Indicators ("Internal Specifications"). Indicators that do not so perform will be replaced subject to the conditions and exceptions below, free of charge, provided that (a) they have been inspected, stored, handled and used in accordance with these General Conditions of Sale and TEMPTIME's directions, (b) notice of the alleged defect is given to TEMPTIME in writing within a reasonable time together with evidence reasonably satisfactory to TEMPTIME of the alleged defect. In addition, TEMPTIME shall be released from all obligations under all warranties if any of the Indicators are modified after delivery to Buyer or if the damage results from any cause other than use in a manner as intended by TEMPTIME including but not limited to accident, disaster, misuse, and abuse. **REPLACEMENT OF INDICATORS CONSTITUTES TEMPTIME'S SOLE OBLIGATION FOR BREACH OF WARRANTY.**

Expiration of Warranties on TEMPTIME HeatMarker® TTI's: All warranties expire with respect to a particular delivery of Heatmarker® TTI's at the later to occur of either (i) or (ii) next following: (i) three (3) years after the date of such delivery, or, (ii) if a longer "outside warranty expiration date" is set forth in the "Quotation" or "Order Acknowledgement" sent from TEMPTIME to Buyer with respect to such TTI's, such longer "outside warranty expiration date."

Expiration of Warranties on TEMPTIME Indicators other than HeatMarker® TTI's, including FreshCheck® TTI's and all THI's: All warranties expire with respect to a particular delivery of Indicators other than Heatmarker® TTI's at the earlier to occur of either (i) or (ii) next following: (i) one (1) year after the date of such delivery, or, if a longer or shorter "outside warranty expiration date" is set forth in the "Quotation" or "Order Acknowledgement" sent from TEMPTIME to Buyer with respect to such Indicators, such longer or shorter "outside warranty expiration date"; or (ii) thirty (30) days after the "end point" (as defined in the Order Specifications) occurs for any of the Indicators in such delivery or, if no Order Specifications are provided with the "Quotation" or "Order Acknowledgement" with respect to such Indicators, thirty (30) days after the "end point" (as defined in the Internal Specifications) occurs with respect to any of the Indicators in such delivery.

Upon expiration of the warranties as provided above, all rights to make claims under the warranties shall cease.

Nothing contained in standard forms used by the parties (including without limitation purchase orders, sales orders, sales confirmations or invoices) shall be construed to modify or amend this Statement of Warranties, which may not be modified or altered except by written instrument duly executed by both parties.

**Storage of Indicators in TEMPTIME's Freezers.** Upon request, TEMPTIME will store Indicators ordered by Buyer in TEMPTIME's freezers for up to two (2) months at no charge. TEMPTIME will issue a final invoice to Buyer when the Indicators are manufactured, tested, stored in TEMPTIME's freezers and available for delivery. For the storage of any customized Indicators, beyond the two (2) month period, TEMPTIME will charge a storage fee of 1.5% of the total cost of the order, per month, until delivery is taken. Buyer shall notify TEMPTIME that it desires a delivery of Indicators stored in the TEMPTIME freezers at least one week in advance. TEMPTIME will assume risk of loss for Indicators that it stores for Buyer for the period of storage but not more than for a period of twelve (12) months.

**Force Majeure.** No failure or omission by TEMPTIME in the performance of any of its obligation hereunder shall be deemed to create any liability if the same shall arise from any cause or causes beyond its control. Such cause or causes beyond its control shall include, but not be limited to, the following events of force majeure: acts of God; acts or omissions of any government or any rules, regulations or orders of any governmental authority or any officer, department, agency or instrumentality thereof; fire; storm; flood; earthquake; insurrection; riot; invasion; strikes; and changes in toxicological or environmental risk. In the event TEMPTIME finds itself unable to perform any of its obligations hereunder, it shall use reasonable efforts to remedy the effects of any such event beyond its control. Upon the happening of any of the aforesaid clauses, TEMPTIME may cancel the orders thereby affected, or may in its discretion delay performance until such cause or causes have been abated.

**Taxes.** Buyer shall be responsible for payment of any and all taxes on Indicators including municipal, state or federal sales, use, personal property, excise import duty, value-added tax or similar taxes and where applicable shall provide TEMPTIME with a tax exemption certificate acceptable to the taxing authorities.

**Certain Rights of TEMPTIME.** If Buyer owes TEMPTIME any past due amount or if Buyer shall have breached these General Conditions of Sale or any other agreement or understanding (written or otherwise) with TEMPTIME or TEMPTIME's agent, or if Buyer's credit should become impaired or unsatisfactory to TEMPTIME, then TEMPTIME may, in its sole discretion, in addition to all other actions and remedies it may take under these General Conditions of Sale or at law, after giving Buyer written notice: (1)

make shipments of undelivered portion of the Indicators for cash against documents, in which event Buyer shall be bound to pay for them in cash or (2) consider any undelivered portion of the Indicators as automatically canceled, or (3) sell in the open market any Indicators not theretofore delivered, with Buyer remaining obligated to TEMPTIME for the difference between the price specified in Buyer's order for the Indicators not theretofore delivered, or if no such price has been specified, TEMPTIME's list price for such Indicators (without giving effect to quantity discounts, if any) on the date of the order and the net price so realized by TEMPTIME.

**Miscellaneous**. Buyer acknowledges that it has read these General Conditions of Sale, understands them and agrees to be bound by their terms, and further agrees that they represent the complete and exclusive statement of the agreement between the parties relating to the subject matter hereof, which supersedes and merges all prior quotations, proposals, understandings and all other agreements, oral and written, between the parties relating to the subject matter hereof. These General Conditions of Sale may not be modified or altered except by a written document duly executed by TEMPTIME and shall not be deemed modified by how TEMPTIME and Buyer have in the past conducted, or will in the future conduct, business with each other or by anything contained in standard forms used by Buyer (including without limitation, Buyer's form of purchase order or other order form).

All orders, these General Conditions of Sale and the rights or obligations of the parties hereto shall be governed by the laws of the State of New Jersey, without giving effect to principles relating to choice of law.

No action in law or equity arising out of the relationship of Buyer and TEMPTIME may be brought by Buyer more than two years after the cause of action has first arisen.

If any of the above provisions are invalid under any applicable statute or rule of law, the remaining provisions shall remain in full force and affect.

TEMPTIME shall have the right to collect from Buyer its reasonable expenses, including attorneys' fees, incurred in enforcing its rights pursuant to a purchase order.

The waiver or failure of TEMPTIME to exercise in any respect any right provided for herein shall not be deemed a waiver of any other right hereunder.

TEMPTIME
The World Leader in Time-Temperature Indicators

# Special World-Wide Pricing Guide for UNICEF Tender Contracts (2007 – 2009)

*This Specific Price List is valid for any delivery from 1 January 2007 to The end of December 2009 for all vaccines except Oral Polio Vaccine*



NOTE: ALL ORDERS ARE SUBJECT TO THE TEMPTIME GENERAL CONDITIONS OF SALE WHICH AMONG OTHER THINGS, CONTAINS DISCLAIMERS OF WARRANTIES AND LIMITATIONS OF DAMAGES. NOTHING IN THIS PRICING GUIDE IS INTENDED TO ALTER THE TEMPTIME GENERAL CONDITIONS OF SALE AS THEY MAY BE REVISED BY TEMPTIME FROM TIME TO TIME.

# Chapter 1.
# Standard Specifications for the UNICEF Tender 2007 - 2009

## 1.1 Definitions:

**Full Label VVM (common label + time-temperature indicator)** – is a customized order specifically manufactured for one vaccine manufacturer, for one specific vaccine and for one specific type of VVM - 30 days @37ºC; 14 days@37ºC; 7 days @37ºC or 2 days@37ºC.

**Dot VVM (time-temperature indicator only)** – is a standard TTI without text, one standard for each specific type of VVM: 30 days @37ºC; 14 days @37ºC; 7 days @37ºC or 2 days@37ºC.

## 1.2 Specifications:

| Specification | Full Label VVM | Dot VVM |
|---|---|---|
| *Minimum Order For One (1) Shipment* | 500,000 | 50,000 |
| *Standard Label Sizes* | 20mm X 44mm<br>57mm X 15mm<br>48mm X 18mm | 10mm dot (circle) |
| *Indicators Per Roll* | 10,000 | 10,000 |
| *Presentations* | 1 | 1 |
| *Rewind Direction* | 1 | 1 |
| *Core Size* | 76mm | 76mm |
| *Shipped by Container* | LD3 (in one shipment) | Insulated Cooler or an LD3 (in one shipment) depending on volume |
| *Number of Label Colors* | 1 | N/A |
| **Payment Terms & Conditions:** Pre-paid; 50% down-payment or Irrevocable Letter of Credit – Payable 30 days after shipment | | |
| **Deliveries:**<br>• *All deliveries are Ex Works TEMPTIME Corporation (Morris Plains, NJ – USA) See the General Conditions of Sale (Chapter 6). Shipment costs are not included in the prices in this price guide (dry ice, specific shipping container rental, inland transportation and air freight are all additional costs).*<br>• *All deliveries for the full label VVM described on page #3 and VVM dots for orders of 500,000 or greater, includes the fixed specific shipment preparation charge for one shipment* | | |
| **Handling Charge:** *The full label prices are established on quantities corresponding to one shipment, which includes the fixed specific shipment preparation charge. If a customer makes a specific request to receive an order in several shipments, the fixed specific shipment preparation charge ($500) will be added to each additional shipment, except if exactly equivalent to the rule in Chapter 3.* | | |

**1.3 Timing:** The pricing is valid for the period of the 2007 – 2009 UNICEF Tender and only for orders linked to the tender, which will be shipped from 1 January 2007 to the end of December 2009.

**1.4 Special Orders** Any order different from these standard specifications will be quoted on a case-by-case basis (See Chapter 5).

## Chapter 2.
## Full Label VVM Prices in US Cents* for the UNICEF Tender 2007 -2009

| Quantity by Shipment | VVM 2<br>2 days @37ºC | VVM7<br>7 days @37ºC | VVM14<br>14 days @37ºC | VVM30<br>30 days @37ºC |
|---|---|---|---|---|
| 4,000,000+ | 4.04 | 5.09 | 5.19 | 5.31 |
| 2,000,000 | 4.27 | 5.25 | 5.38 | 5.46 |
| 1,000,000 | 4.51 | 5.51 | 5.59 | 5.82 |
| 500,000 | 5.05 | 6.11 | 6.22 | 6.36 |

Basic Price includes specific packaging & handling costs

***The price, in US cents, corresponds to the Standard Specifications defined on page 2 – Any order or request different from the Standard Specifications will be considered as a special request and quoted on a case-by-case basis (ex: sequential numbering).***

### Full Label VVM7 - Pricing Example:

| Quantity by Shipment | VVM Type | # Per Roll | Basic Price | Total Costs By Shipment |
|---|---|---|---|---|
| 4 million | VVM7<br>7 days @37ºC | 10,000 per roll | 5.09 | $203,600 |
| 2 million | VVM7<br>7 days @37ºC | 10,000 per roll | 5.25 | $105,000 |
| 1 million | VVM7<br>7 days @37ºC | 10,000 per roll | 5.51 | $55,100 |
| 500,000 | VVM7<br>7 days @37ºC | 10,000 per roll | 6.11 | $30,550 |

# Chapter 3.

## Dot Prices in US Cents for the UNICEF Tender 2007 -2009

| Quantity by Shipment | VVM2<br>2 days @37ºC | VVM7<br>7 days @37ºC | VVM14<br>14 days @37ºC | VVM30<br>30 days @37ºC |
|---|---|---|---|---|
| 4,000,000+ | 3.39 | 4.43 | 4.53 | 4.58 |
| 2,000,000 | 3.56 | 4.59 | 4.69 | 4.74 |
| 1,000,000 | 3.69 | 4.72 | 4.83 | 4.89 |
| 500,000 | 3.84 | 4.87 | 4.97 | 5.04 |
| Between 50,000 and 500,000 | 3.84 | 4.87 | 4.97 | 5.04 |

Basic Price includes specific packaging & handling costs

***Rule for Packaging and Handling:*** ***TEMPTIME Corporation will add a fixed specific shipment preparation charge of $500 for each order below 500,000 units that are not shipped with another larger order. If orders below 500,000 are shipped with another order above 500,000 the specific shipment preparation charge will be waived***

***If two (2) orders (below 500,000 in total) are shipped together, TEMPTIME will add only one (1) $500 fixed charge for specific shipment preparation.***

***The costs of dry ice, shipping container, inland freight and/or - airfreight are not included in the prices above.***

## Dot VVM30 - Pricing Example:

| Quantity by Shipment | VVM Type | # Per Roll | Basic Price | Total Costs By Shipment |
|---|---|---|---|---|
| 4 million | VVM30<br>30 days @37ºC | 10,000 per roll | 4.58 | $183,200 |
| 2 million | VVM30<br>30 days @37ºC | 10,000 per roll | 4.74 | $94,800 |
| 1 million | VVM30<br>30 days @37ºC | 10,000 per roll | 4.89 | $48,900 |
| 500,000 | VVM30<br>30 days @37ºC | 10,000 per roll | 5.04 | $25,200 |
| 100,000 shipped alone | VVM30<br>30 days @37ºC | 10,000 per roll | 5.04 + $500 Handling Fee | $5,040 + $500 = **$5,540** |
| 100,000 shipped with another order of 500,000 or larger | VVM30<br>30 days @37ºC | 10,000 per roll | 5.04 | $5,040 |

# Chapter 4.
# Conditions of Delivery

4.1 Type of VVM
TEMPTIME will provide the VVM (VVM30: VVM14: VVM7: VVM2) only after the WHO has approved the use of the VVM for the vaccine. WHO approval is required for the first order of VVMs for each new vaccine.

4.2 Conditions of Delivery for VVMs
**TEMPTIME will provide a final delivery date upon receipt of (1) the final customer approved artwork, (2) VVM category approval by WHO, and (3) receipt of the down payment or Letter of Credit. If only one of the 3 items is missing, the order cannot be confirmed**.

4.3 Shipment Lead Time After Confirmation of the Order: Lead times are very different for the dot VVM, which are generally stored in TEMPTIME inventory and can be shipped in one - three weeks, and the full label VVM that requires a customized manufacturing for each order.

| | VVM Type | Dot VVM | Full Label VVM |
|---|---|---|---|
| ***Normal Manufacturing Lead Times*** | VVM2 | **1 – 3 weeks** | **3 to 5 weeks** |
| | VVM7 | **1 – 3 weeks** | **3 to 6 weeks** |
| | VVM14 | **1 – 3 weeks** | **4 to 7 weeks** |
| | VVM30 | **1 – 3 weeks** | **4 to 7 weeks** |

4.4 Certificate of Analysis: TEMPTIME Corporation supplies a Certificate of Analysis for each lot showing conformance with the WHO Specification for Vaccine Vial Monitors (VVM) E6/IN5, 25 March 2002 using TEMPTIME Testing Protocol ***#P023-C – Protocol for Testing and Releasing a Lot of HEATmarker™ Vaccine Vial Monitors at 37ºC*** dated 23 January 2002 or ***#P025 Protocol for Testing and Releasing a Lot of HEATmarker™ Vaccine Vial Monitors at 45ºC*** dated 5 July 2004 and agreed by WHO that TEMPTIME can use under our responsibility.

4.5 Packaging: Each Shipment has a specific and proper packaging of the consignment with dry ice in accordance with the TEMPTIME Corporation General Conditions of Sale.

# Chapter 5
# Special Requests (Additional Costs) (To be determined on a case-by-case basis)

## 5.1 Special Requests

Each "special request" will have an additional cost assigned to it by TEMPTIME. Examples of "special requests" that TEMPTIME may consider are:

(1) Full Label Orders Below 500,000 Units

(2) Size differential from the three (3) standard full label sizes

(3) Indicators per roll are less than 10,000

(4) Two (2) or more full label presentations for the same order

(5) Additional Rewinding

(6) Core Size different from 76mm standard

(7) Two (2) colors or more on a full label

**(8) Sequential Numbering:**

- **a. Available only with a full label**
- **b. Minimum additional cost of 0.22 cents per indicator**
- **c. Additional lead time required of 2- 4 weeks depending on quantities**

(9) Requests for Additional Liner at Beginning or End of the Roll

(10) Size of Label Greater than 880mm²

(11) Urgent / Rush Order

## 5.2 Quotes:

TEMPTIME will respond to any special request within a two (2) week timeframe by issuing a specific quotation.

## 6. GENERAL CONDITIONS OF SALE

### (TIME-TEMPERATURE INDICATORS)

**The Purchase and Sale.** Subject to the following terms and conditions (the "Conditions"), TEMPTIME Corporation agrees to sell to Buyer the time-temperature indicator products ("TTI's") set forth on the attached order/confirmation or on an order/confirmation which refers to these General Conditions of Sale.

**Acceptance or Non-acceptance.** Each purchase of TTI's, or any part thereof, by Buyer shall be made by an order from Buyer to TEMPTIME Corporation setting forth the purchase price and the date for shipment of the TTI's. No order, whether written or oral, shall be accepted unless confirmed in writing by TEMPTIME Corporation. TEMPTIME Corporation may accept or reject such order, at its sole discretion. If an order is accepted and confirmed, then the terms and conditions hereinafter set forth shall be applicable to each such order.

**Payment Terms.** Unless TEMPTIME Corporation has otherwise provided in a writing specifically relating to a Buyer's order, for all transactions, TEMPTIME Corporation requires either a Letter of Credit acceptable to TEMPTIME Corporation for the benefit of TEMPTIME Corporation or a 50% down payment and acceptance of all orders shall be subject to receipt by TEMPTIME Corporation of either such down payment or the opening of such a Letter of Credit. Final and full payment is due and payable thirty (30) days after the date of TEMPTIME Corporation' final invoice and, if the Buyer has provided a Letter of Credit, TEMPTIME Corporation will draw upon the Letter of Credit at such time for the amount then due and payable unless the Buyer has otherwise paid such amount to TEMPTIME Corporation. All payments shall be made in U.S. dollars.

**Invoices.** TEMPTIME Corporation will issue a final invoice to the Buyer on the day the TTI's are shipped.

**Interest on Past Due Accounts.** Interest at the maximum legal rate or 1 1/2% per month, whichever is lower, may be charged by TEMPTIME Corporation on past due accounts. Such interest is due and payable by Buyer on receipt of an invoice therefor.

**Tolerance on Quantity.** When the TTI's are custom products (that is, products (i) other than those that contain only a time-temperature indicator (without text) or (ii) which require non-standard TTI chemistry and/or manufacturing processes), TEMPTIME Corporation and the Buyer agree that TEMPTIME Corporation may manufacture for the Buyer TTI's pursuant to Buyer's order in quantities of between 100% - 110% of the amount ordered. The final invoice will reflect the actual quantity of custom products manufactured within the agreed tolerance. When the TTI's are other than a custom product, TEMPTIME Corporation will produce TTI's in accordance with Buyer's order.

**Delivery and Risk of Loss.** All deliveries of TTI's are EXW TEMPTIME Corporations' manufacturing facility – Morris Plains (USA) (applying International Chamber of Commerce INCOTERMS 2000). The mode of shipment, including the carrier, shall be determined by Buyer. Buyer may ask TEMPTIME Corporation to arrange for shipping or recommend or choose a carrier or, should Buyer fail to instruct TEMPTIME Corporation, TEMPTIME Corporation will choose the carrier. Whether or not TEMPTIME Corporation so arranges shipping, Buyer shall bear the risk of loss upon TEMPTIME Corporation' placing the TTI's at the disposal of the Buyer or the carrier at TEMPTIME Corporation' manufacturing facility and, thereafter, TEMPTIME Corporation shall have no liability for loss or damage, whether incidental, consequential, direct, indirect, special or punitive, whether occurring from delays or damage, or otherwise. In all circumstances, Buyer shall pay the expense of shipment from TEMPTIME Corporation' manufacturing facility and if TEMPTIME Corporation shall incur such costs, Buyer shall reimburse TEMPTIME Corporation therefor upon the issuance by TEMPTIME Corporation to Buyer of an invoice with respect thereto.

**Inspection.** Promptly after the TTI's are delivered, and on the day of such delivery, Buyer shall inspect such TTI's for spoilage and damage. The failure of Buyer to inspect such TTI's promptly and on the day of delivery, and/or failure of Buyer to notify TEMPTIME Corporation of spoilage and/or damage of such TTI's within forty-eight (48) hours after delivery, shall operate as a full and complete waiver of all claims by Buyer that such TTI's are spoiled and/or damaged.

**Use and Storage of TTI's.** ***TTI's are not intended for use in direct contact with material intended for human consumption. Accordingly, Buyer agrees not to use the TTI's in such manner and shall indemnify and hold TEMPTIME Corporation harmless from any damages, claims or losses (including reasonable attorneys' fees and expenses) arising out of Buyer's breach of its obligation under this paragraph, including, without limitation, any violation of laws, rules or regulations applicable to materials and products for human consumption.***

Buyer shall not use TTI's that have spoiled or are damaged. If Buyer nevertheless uses such TTI's, TEMPTIME Corporation shall have no liability for any damages suffered in connection therewith and Buyer hereby indemnifies TEMPTIME Corporation against the same. Unless otherwise specified on the box in which the TTI's are packaged for delivery, all TTI's shall be stored by the Buyer at or below –24°C and in the absence of all light, and/or under such other conditions as TEMPTIME Corporation shall direct. Buyer shall "use" (meaning, apply the TTI to Buyer's product) all TTI's delivered to Buyer on or before the "use by" date shown with respect to the TTI's on the box in which the TTI's are packaged for delivery. If any of the TTI's fail to be so stored or used, TEMPTIME Corporation shall have no liability to Buyer for damages suffered in connection therewith, and Buyer hereby indemnifies TEMPTIME Corporation against the same, and TEMPTIME Corporation not have any obligation for replacement of such TTI's.

**DISCLAIMER OF WARRANTIES AND LIMITATION OF DAMAGES AS TO TTI'S.**

**EXCEPT AS SET FORTH ON THE NEXT PAGE UNDER THE HEADING "STATEMENT OF LIMITED WARRANTY," TEMPTIME CORPORATION SPECIFICALLY EXCLUDES ALL WARRANTIES, EXPRESS OR IMPLIED, INCLUDING BUT NOT LIMITED TO WARRANTIES THAT THE TTI'S ARE MERCHANTABLE AND THAT THE TTI'S ARE FIT FOR ANY PARTICULAR PURPOSE. TEMPTIME CORPORATION SHALL HAVE NO LIABILITY FOR MONETARY DAMAGES RESULTING FROM DEFECTS IN THE TTI'S, WHETHER OR NOT COVERED BY WARRANTY, INCLUDING BUT NOT LIMITED TO DAMAGES FOR LOSS OF PROFITS OR INCIDENTAL, CONSEQUENTIAL, DIRECT, INDIRECT, SPECIAL OR PUNITIVE DAMAGES.**

**Statement of Limited Warranty.** All TTI's are warranted to Buyer to perform substantially in conformance with the specifications provided with the "Quotation" or "Order Acknowledgement" sent from TEMPTIME Corporation to Buyer with reference to such TTI's (the "Order Specifications") or, if no such specifications are so provided, in accordance with TEMPTIME Corporation' internal specifications applicable to such TTI's ("Internal Specifications"). TTI's that do not so perform will be replaced subject to the conditions and exceptions below, free of charge, provided that (a) they have been inspected, stored, handled and used in accordance with these General Conditions of Sale and TEMPTIME Corporation' directions, (b) notice of the alleged defect is given to TEMPTIME Corporation in writing within a reasonable time together with evidence reasonably satisfactory to TEMPTIME Corporation of the alleged defect. In addition, TEMPTIME Corporation shall be released from all obligations under all warranties if any of the TTI's are modified after delivery to Buyer or if the damage results from any cause other than use in a manner as intended by TEMPTIME Corporation including but not limited to accident, disaster, misuse, and abuse. **REPLACEMENT OF TTI'S CONSTITUTES TEMPTIME CORPORATION' SOLE OBLIGATION FOR BREACH OF WARRANTY.**

Expiration of Warranties on TEMPTIME Corporation HeatMarker® TTI's: All warranties expire with respect to a particular delivery of Heatmarker® TTI's at the later to occur of either (i) or (ii) next following: (i) three (3) years after the date of such delivery, or, (ii) if a longer "outside warranty expiration date" is set forth in the "Quotation" or "Order Acknowledgement" sent from TEMPTIME Corporation to Buyer with respect to such TTI's, such longer "outside warranty expiration date."

Expiration of Warranties on TEMPTIME Corporation TTI's other than HeatMarker® TTI's, including FreshCheck® TTI's: All warranties expire with respect to a particular delivery of TTI's other than Heatmarker® TTI's at the earlier to occur of either (i) or (ii) next following: (i) one (1) year after the date of such delivery, or, if a longer or shorter "outside warranty expiration date" is set forth in the "Quotation" or "Order Acknowledgement" sent from TEMPTIME Corporation to Buyer with respect to such TTI's, such longer or shorter "outside warranty expiration date"; or (ii) thirty (30) days after the "end point" (as defined in the Order Specifications) occurs for any of the TTI's in such delivery or, if no Order Specifications are provided with the "Quotation" or "Order Acknowledgement" with respect to such TTI's, thirty (30) days after the "end point" (as defined in the Internal Specifications) occurs with respect to any of the TTI's in such delivery.

Nothing contained in standard forms used by the parties (including without limitation purchase orders, sales orders, sales confirmations or invoices) shall be construed to modify or amend this Statement of Warranties, which may not be modified or altered except by written instrument duly executed by both parties.

**Storage of TTI's in TEMPTIME Corporation' Freezers.** Upon request, TEMPTIME Corporation will store TTI's ordered by Buyer in TEMPTIME Corporation freezers for up to two (2) months at no charge. TEMPTIME Corporation will issue a final invoice to Buyer when the TTI's are manufactured, tested, stored in TEMPTIME Corporation' freezers and available for delivery. For the storage of any customized TTI, beyond the two (2) month period, TEMPTIME Corporation will charge a storage fee of 1.5% of the total cost of the order, per month, until delivery is taken. Buyer shall notify TEMPTIME Corporation that it desires a delivery of their TTI's stored in the TEMPTIME Corporation freezers at least one week in advance. TEMPTIME Corporation will assume risk of loss for TTI's that it stores for Buyer for the period of storage but not more than for a period of twelve (12) months.

**Force Majeure.** No failure or omission by TEMPTIME Corporation in the performance of any of its obligation hereunder shall be deemed to create any liability if the same shall arise from any cause or causes beyond its control. Such cause or causes beyond its control shall include, but not be limited to, the following events of force majeure: act of God; acts or omissions of any government or any rules, regulations or orders of any governmental authority or any officer, department, agency or instrumentality thereof; fire; storm; flood; earthquake; insurrection; riot; invasion; strikes; and changes in toxicological or environmental risk. In the event TEMPTIME Corporation finds itself unable to perform any of its obligations hereunder, it shall use reasonable efforts to remedy the effects of any such event beyond its control. Upon the happening of any of the aforesaid clauses, TEMPTIME Corporation may cancel the orders thereby affected, or may in its discretion delay performance until such cause or causes have been abated.

**Taxes.** Buyer shall be responsible for payment of any and all taxes on TTI's including municipal, state or federal sales, use, personal property, excise import duty, value-added tax or similar taxes and where applicable shall provide TEMPTIME Corporation with a tax exemption certificate acceptable to the taxing authorities.

**Certain Rights of TEMPTIME Corporation.** If Buyer owes TEMPTIME Corporation any past due amount or if Buyer shall have breached these Conditions or any other agreement or understanding (written or otherwise) with TEMPTIME Corporation or TEMPTIME Corporation' agent, or if Buyer's credit should become impaired or unsatisfactory to TEMPTIME Corporation, then TEMPTIME Corporation may in its sole discretion, in addition to all other actions and remedies it may take under these Conditions or at law, after giving Buyer written notice: (1) make shipments of undelivered portion of the TTI's for cash against documents, in which event Buyer shall be bound to pay for them in cash or (2) consider any undelivered portion of the TTI's as automatically

canceled, or (3) sell in the open market any TTI's not theretofore delivered, crediting Buyer's account with the difference between the net price thus realized and the price specified in Buyer's order for the TTI's not theretofore delivered, or if no such price has been specified, TEMPTIME Corporation' list price for such TTI's (without giving effect to quantity discounts, if any) on the date of the order.

**Miscellaneous**. Buyer acknowledges that it has read these Conditions understands them and agrees to be bound by their terms, and further agrees that they represent the complete and exclusive statement of the agreement between the parties relating to subject matter hereof, which supersedes and merges all prior quotations, proposals, understandings and all other agreements, oral and written, between the parties relating to the subject matter hereof. These Conditions may not be modified or altered except by a written document duly executed by TEMPTIME Corporation and shall not be deemed modified by how TEMPTIME Corporation and Buyer have in the past conducted, or will in the future conduct, business with each other or by anything contained in standard forms used by Buyer (including without limitation, Buyer's form of purchase order or other order form).

All orders, these Conditions and the rights or obligations of the parties hereto shall be governed by the laws of the State of New Jersey, without giving effect to principles relating to choice of law.

No action in law or equity arising out of the relationship of Buyer and TEMPTIME Corporation may be brought by Buyer more than two years after the cause of action has first arisen.

If any of the above provisions are invalid under any applicable statute or rule of law, the remaining provisions shall remain in full force and affect.

TEMPTIME Corporation shall have the right to collect from Buyer its reasonable expenses, including attorneys' fees, incurred in enforcing its rights pursuant to a purchase order.

The waiver or failure of TEMPTIME Corporation to exercise in any respect any right provided for herein shall not be deemed a waiver of any other right hereunder.